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(54) **COMPOSITIONS AND METHODS FOR THE TREATMENT OR PREVENTION OF HUMAN ADENOVIRUS-36 INFECTION**

(58) **Field of Classification Search**

None

See application file for complete search history.

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(56) **References Cited**

U.S. PATENT DOCUMENTS

4,775,622	A	10/1988	Hitzeman et al.
5,234,830	A	8/1993	Oshima et al.
5,310,654	A	5/1994	Isberg et al.
5,413,914	A	5/1995	Franzusoff
5,830,463	A	11/1998	Duke et al.
5,858,378	A	1/1999	Bostwick
5,919,651	A	7/1999	Hitzeman et al.

(Continued)

FOREIGN PATENT DOCUMENTS

EP	0414404	2/1991
FR	2486400	1/1982

(Continued)

OTHER PUBLICATIONS

Atkinson et al., "Human adenovirus-36 is associated with increased body weight and paradoxical reduction of serum lipids," International Journal of Obesity, 29: 281-286 (2005).*

(Continued)

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CPC **A61K 39/235** (2013.01); **A61K 39/12** (2013.01); **A61K 2039/523** (2013.01); **C12N 2710/10334** (2013.01)

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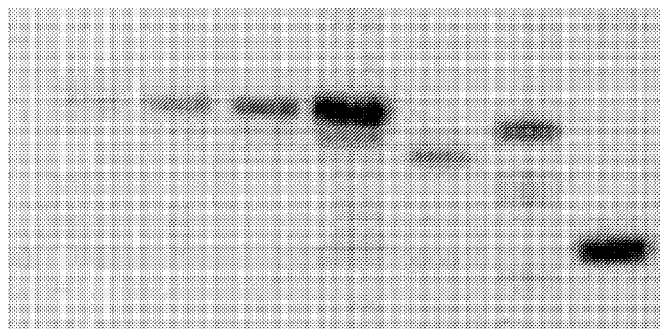
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ABSTRACT

Disclosed are fusion proteins, recombinant nucleic acid molecules, and therapeutic compositions, including yeast-based immunotherapy compositions, for use in the diagnosis, prevention and treatment of adenovirus-36 (Ad-36) infection and sequela thereof.

20 Claims, 15 Drawing Sheets

NS3-HIS(ng)
25 50 100 200 FIB HEX CRAG



(56)

References Cited

U.S. PATENT DOCUMENTS

7,083,787	B2	8/2006	Duke et al.	
7,439,042	B2	10/2008	Duke et al.	
7,465,454	B2	12/2008	Franzusoff et al.	
2002/0044948	A1	4/2002	Khleif et al.	
2003/0035810	A1	2/2003	Caplan	
2004/0166122	A1 *	8/2004	Evans et al.	424/204.1
2007/0172503	A1	7/2007	Selitreffnikoff et al.	
2007/0224208	A1	9/2007	Guo et al.	
2008/0003239	A1 *	1/2008	Duke et al.	424/206.1
2009/0142367	A1	6/2009	Franzusoff et al.	
2010/0034840	A1	2/2010	Apelian et al.	
2010/0111912	A1	5/2010	Apelian et al.	
2010/0189749	A1	7/2010	Franzusoff et al.	
2011/0008295	A1 *	1/2011	Roy et al.	424/93.6
2011/0256098	A1	10/2011	Apelian et al.	
2012/0321664	A1	12/2012	Bellgrau et al.	

FOREIGN PATENT DOCUMENTS

JP	2010-254721	11/2010
WO	WO 2006/044923	4/2006
WO	WO 2007/092792	8/2007
WO	WO 2009/073104	6/2009
WO	WO 2010/011440	1/2010
WO	WO 2010/065626	6/2010
WO	WO 2011/115914	9/2011
WO	WO 2012/019127	2/2012
WO	WO 2012/083302	6/2012
WO	WO 2012/109404	8/2012
WO	WO 2012/125998	9/2012
WO	WO 2012/174220	12/2012
WO	WO 2013/025972	2/2013

OTHER PUBLICATIONS

Liu et al., "Expression, purification, and characterization of hepatitis B virus surface antigens (HBsAg) in yeast *Pichia Pastoris*," Appl. Biochem. Biotechnol. 158(2): 432-44 (2009).*

Rock et al., "Natural endogenous adjuvants," Springer Semin Immunol 26:231-246 (2005).*

Toth et al., "Adenovirus immunoregulatory E3 proteins prolong transplants of human cells in immunocompetent mice," Virus Research 108 149-159 (2005).*

Sharma et al., "Adenovirus E3 proteins help tumors to evade innate and adaptive immune responses," Cancer Biology & Therapy 8:12: 1133-1135 (2009).*

Arnold et al., "Genomic characterization of human adenovirus 36, a putative obesity agent," Virus Research, May 2010, vol. 149, No. 2, pp. 152-161.

Bizzini et al., "Use of live *Saccharomyces cerevisiae* cells as a biological response modifier in experimental infections," FEMS Microbiology Immunology, 1990, vol. 64, pp. 155-168.

Brake et al., "alpha-Factor-directed synthesis and secretion of mature foreign proteins in *Saccharomyces cerevisiae*," Proceedings of the National Academy of Sciences USA, Aug. 1984, vol. 81, pp. 4642-4646.

Eto et al., "Immunization with recombinant *Escherichia coli* expressing retinal S-antigen-induced experimental autoimmune uveitis (EAU) in Lewis rats", Cellular Immunology, vol. 147, No. 1 Mar. 1993, pp. 203-214.

Franzusoff, A. et al. "Yeasts Encoding Tumour Antigens in Cancer Immunotherapy," Expert Opinion on Biological Therapy, Apr. 2005, vol. 5, No. 4, pp. 565-575.

Franzusoff et al. "Biochemical and Genetic Definition of the Cellular Protease Required for HIV-1 gp160 Processing," The Journal of Biological Chemistry, Feb. 1995, vol. 270, No. 7, pp. 3154-3159.

Fujita et al. "Studies in the development of Japanese encephalitis vaccine: expression of virus envelope glycoprotein V3 (E) gene in yeast," Bulletin of the World Health Organization, Feb. 1987, vol. 65, No. 3, pp. 303-308.

Lu, et al., "Mutation-Selective Tumor Remission with Ras-Targeted, Whole Yeast-Based Immunotherapy," Cancer Research, 2004, vol. 64, pp. 5084-5088.

Klepfer et al. "Characterization of rabies glycoprotein expressed in yeast," Archives of Virology, 1993, vol. 128, pp. 269-286.

Krishnapuram et al. "Infectivity period of mice inoculated with human adenoviruses," Lab Anim., Apr. 2011, vol. 45, No. 2, pp. 103-108 (Abstract Only).

Moore et al., "Novel yeast-based vaccine 1-40, against HIV-SF2 gp160 promotes a cytotoxic 43-62 cell response," FASEB Journal (online), vol. 10, No. 6, 1996, p. A1473, ZP002186594, Joint Meeting of the American Society for Biochemistry and Molecular Biology, the American Society for Investigative Pathology and the American Association of Immunologists; New Orleans, LA, USSA; Jun. 2-6, 1996.

Na et al. "Infectobesity: a New Area for Microbiological and Virological Research," Journal of Bacteriology and Virology, Jun. 2011, vol. 41, No. 2, pp. 65-76.

Robinson et al. "The E3 CR1-gamma gene in human adenoviruses associated with epidemic keratoconjunctivitis," Virus Research, Sep. 2011, vol. 160, No. 1-2, pp. 120-127.

Schreuder et al. "Yeast expressing hepatitis B virus surface antigen determinants on its surface: implications for a possible oral vaccine," Vaccine, Apr. 1996, vol. 14, No. 5, pp. 383-388.

Sinai et al. "Enhancement of Resistance to Infectious Diseases by Oral Administration of Brewers Yeast," Infection and Immunity, May 1974, vol. 9, No. 5, pp. 781-787.

Stubbs, et al., "Whole Recombinant Yeast Vaccine Activates Dendritic Cells and Elicits Protective Cell-Mediated Immunity," National Medicine, May 2001, vol. 7, No. 5, pp. 1-5.

Torres et al. "The Revolution in Viral Genomics as Exemplified by the Bioinformatic Analysis of Human Adenoviruses," Viruses, Jul. 2010, vol. 2, No. 7, pp. 1367-1381.

UniProt Direct Submission D4N3K1_9ADEN. [Retrieved from the Internet Jul. 21, 2012: <www.uniprot.org/uniprot/D4N3K1.txt?version+1>] 1 page.

Valenzuela et al. "Antigen engineering in yeast: Synthesis and assembly of hybrid hepatitis B surface antigen—Herpes simplex 1 gD particles", Bio/Technology, Apr. 1985, vol. 3, 323-326.

International Search Report and Written Opinion for International (PCT) Patent Application No. PCT/US11/65868, mailed Aug. 3, 2012 13 pages.

International Preliminary Report on Patentability for International (PCT) Patent Application No. PCT/US2011/065868, mailed Jun. 27, 2013 9 pages.

Extended European Search Report and Search Opinion for European Patent Application No. 11848223.1, dated Sep. 4, 2014, 11 pages.

* cited by examiner

Fig. 1

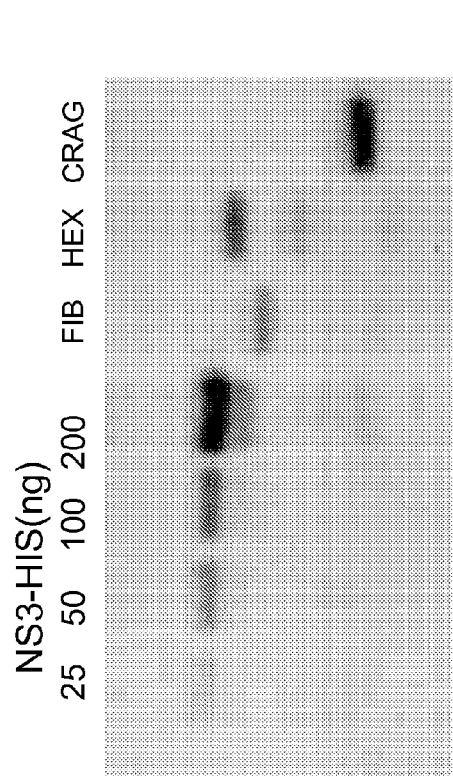


Fig. 2

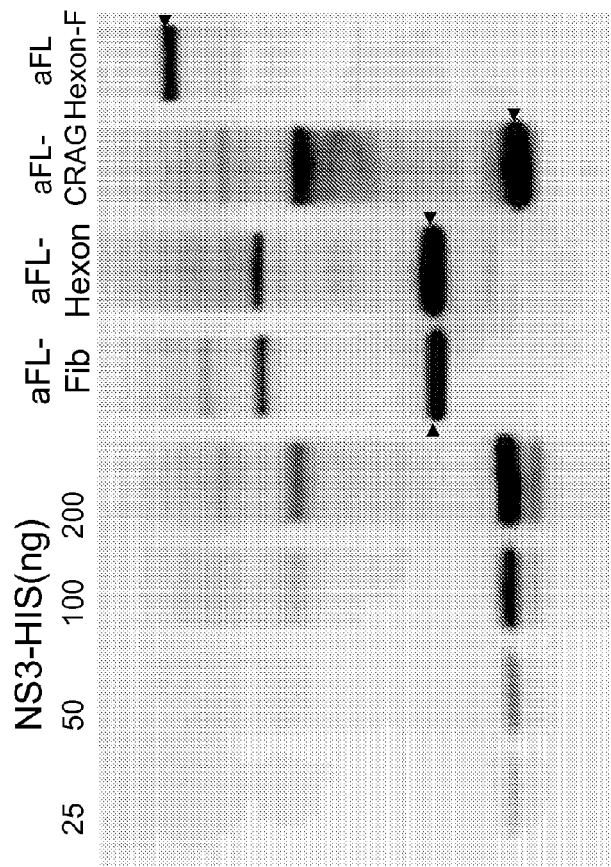


Fig. 3

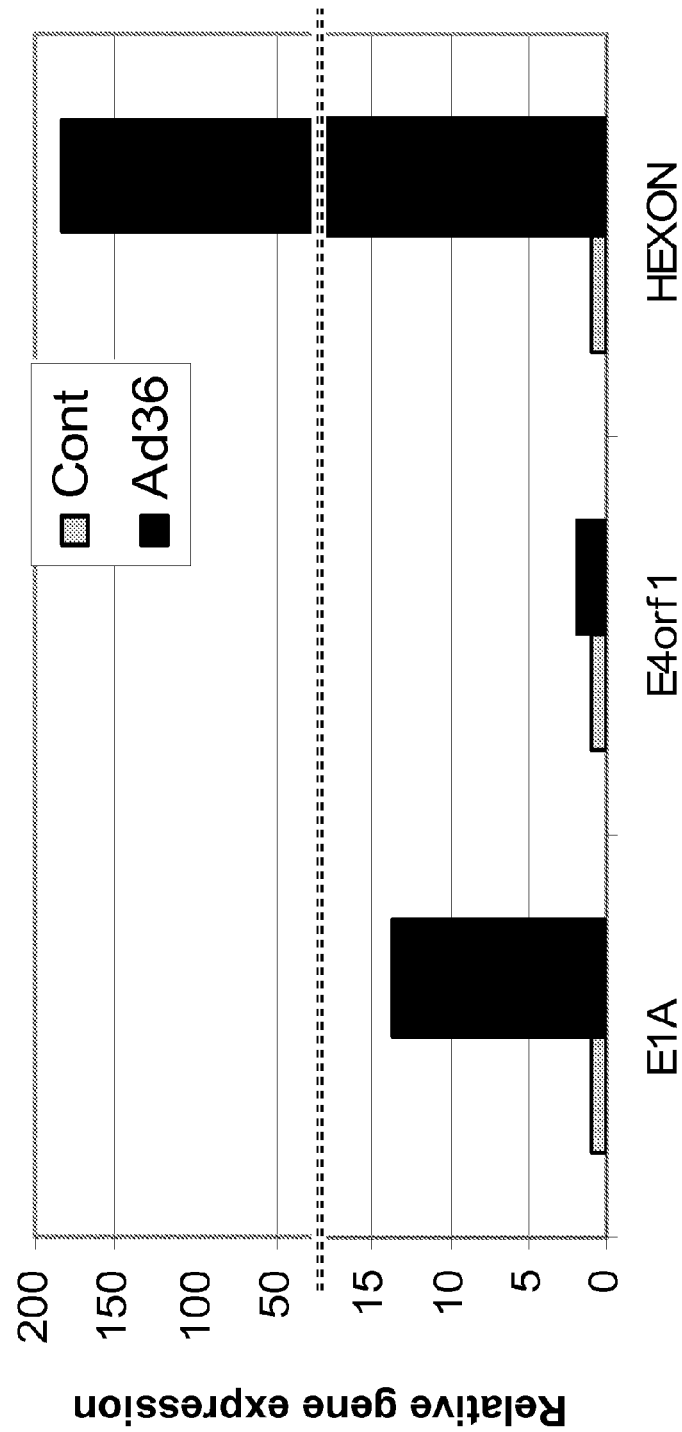


Fig. 4

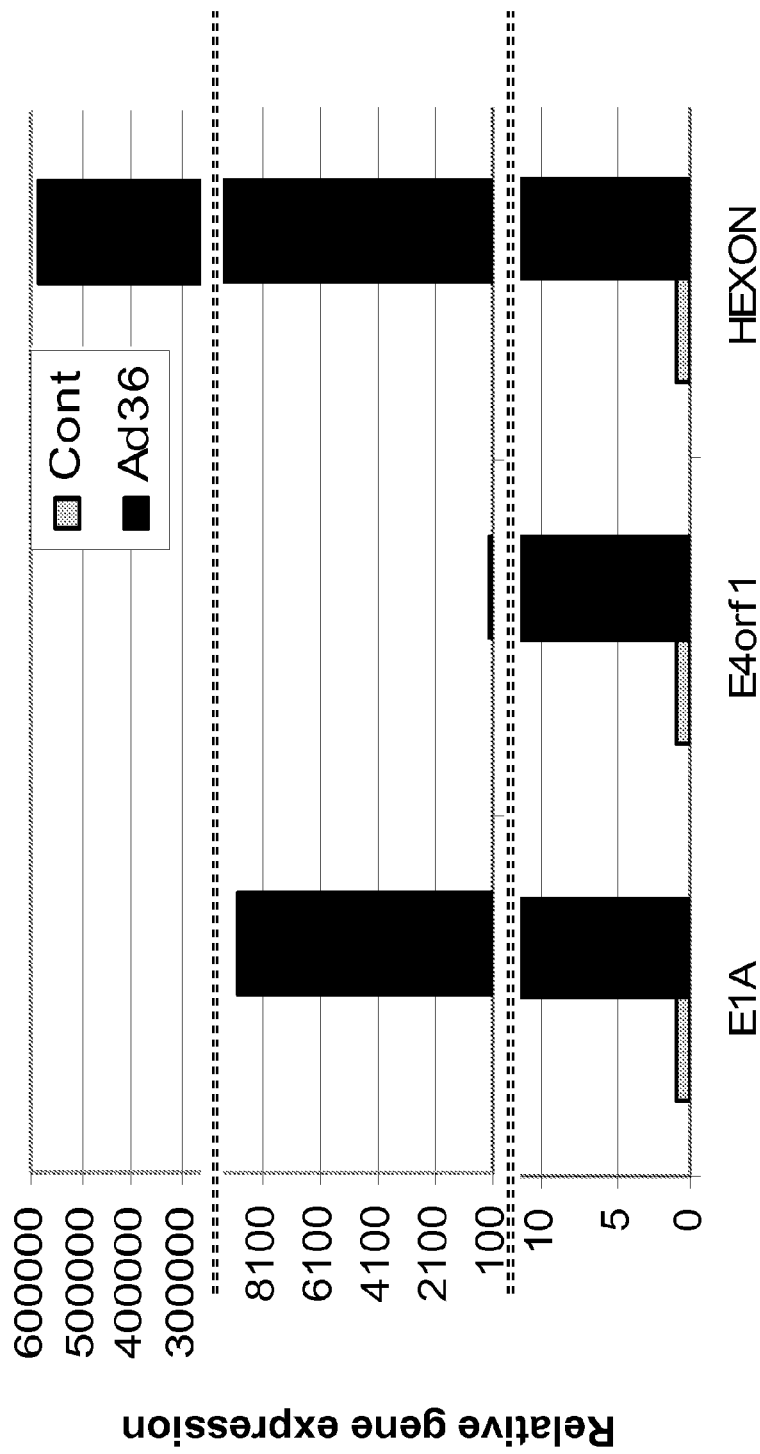
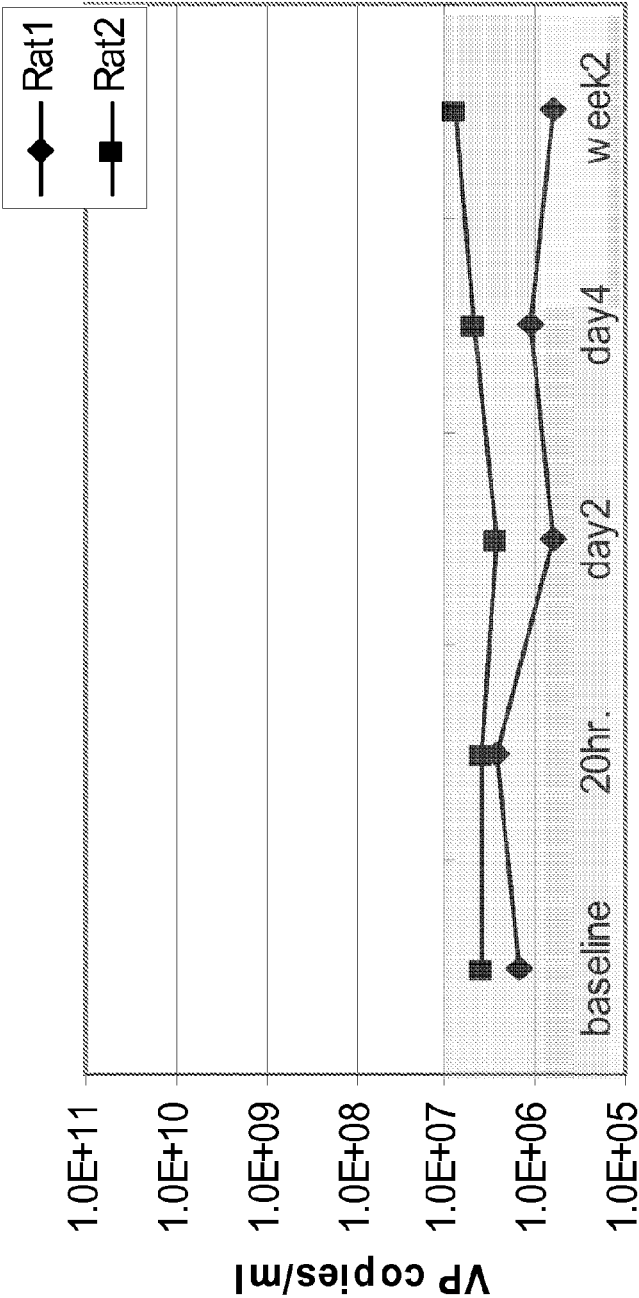
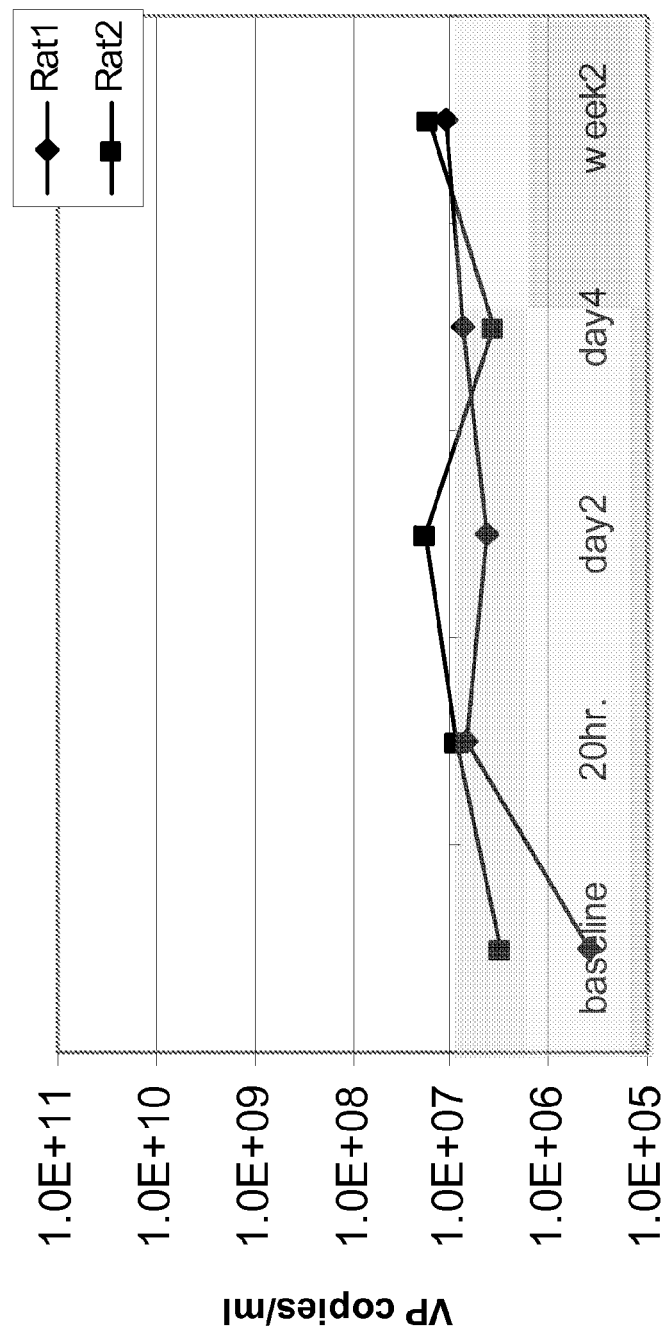


Fig. 5



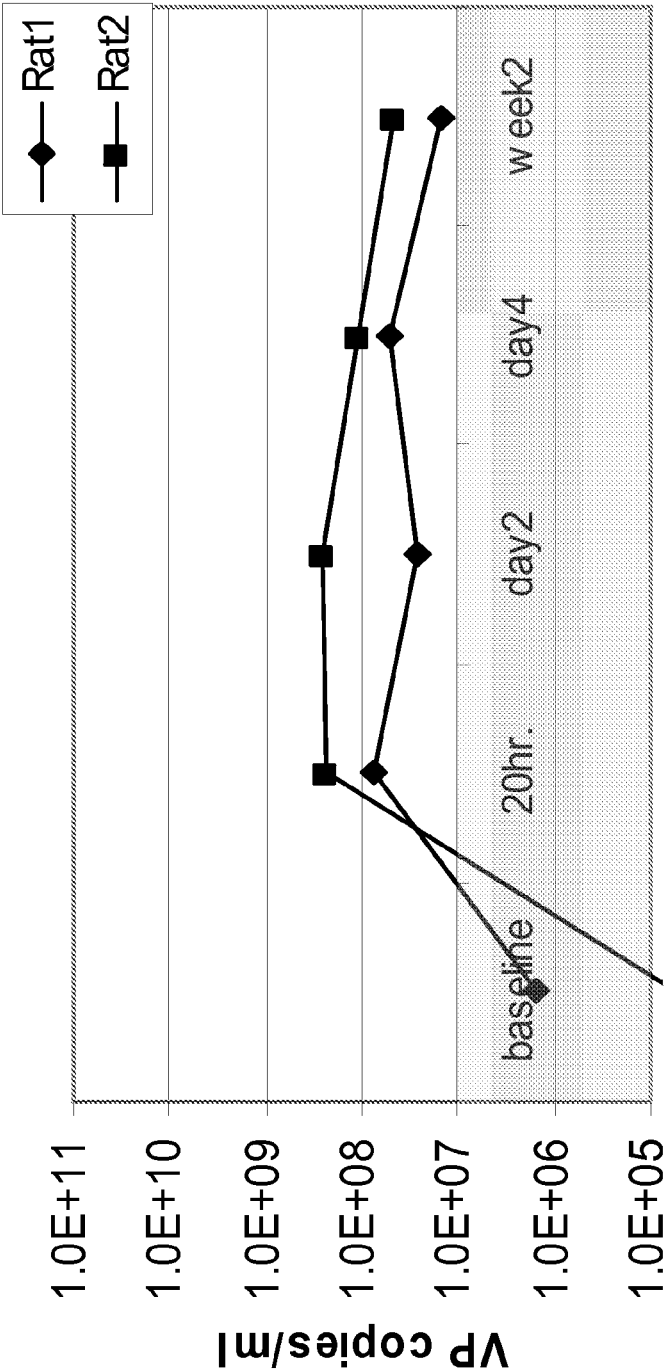
Time - Mock Control

Fig. 6



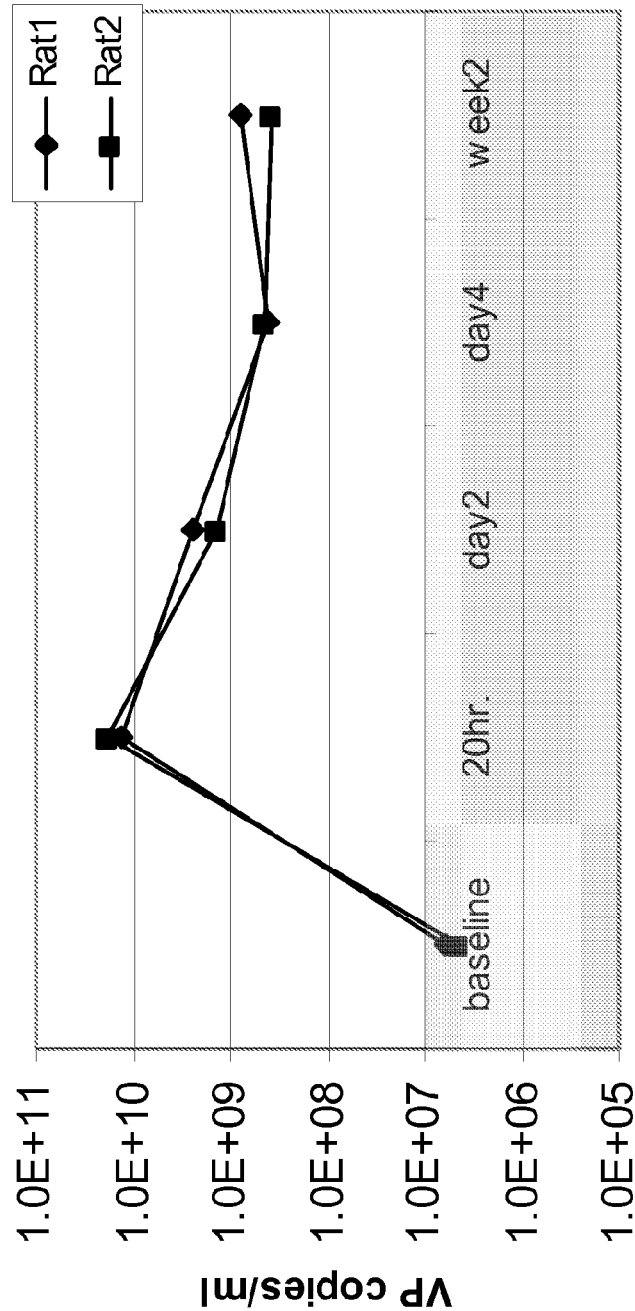
Time Post-Ad36 Injection - 10⁷ PFU Ad36

Fig. 7



Time Post-Ad36 Injection - 10⁸ PFU Ad36

Fig. 8



Time Post-Ad36 Injection - 10⁹ PFU Ad36

Fig. 9

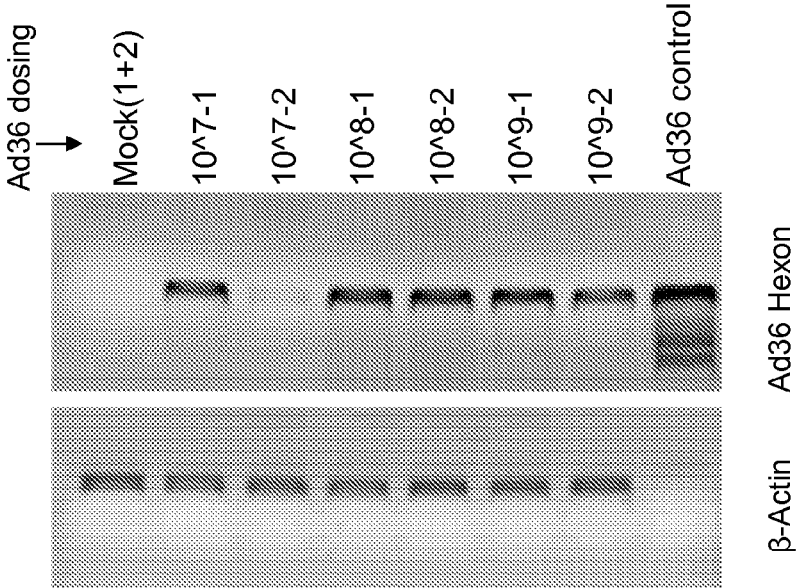


Fig. 10

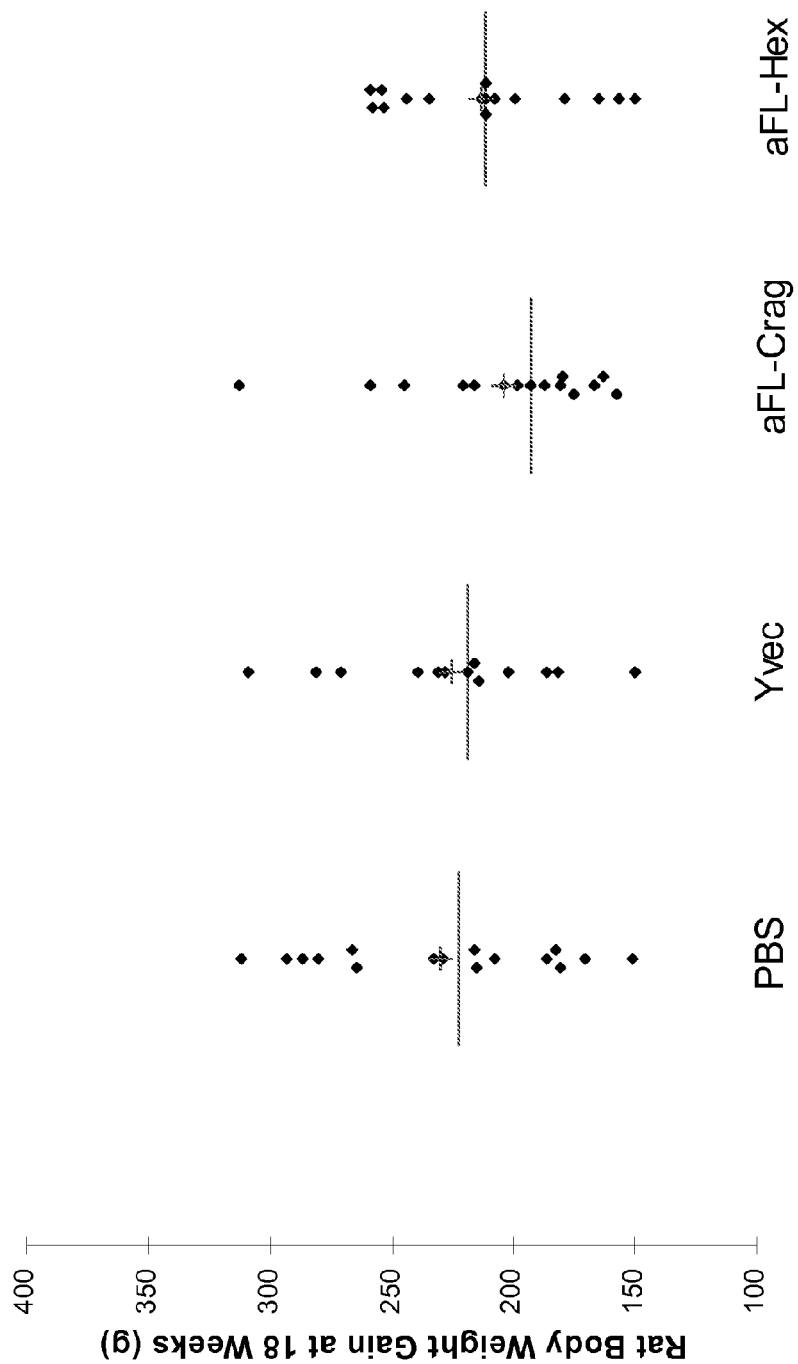


Fig. 11

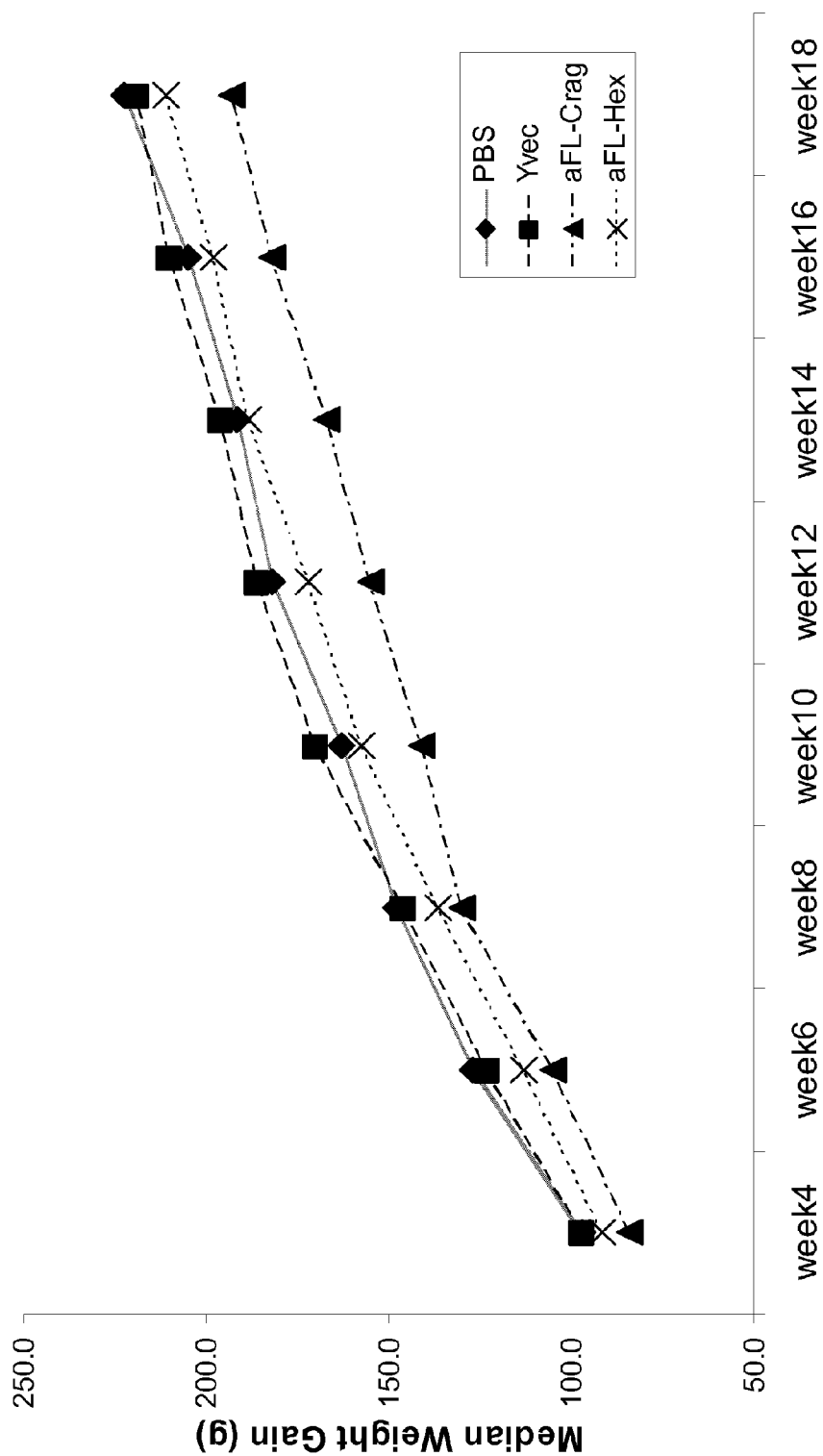


Fig. 12

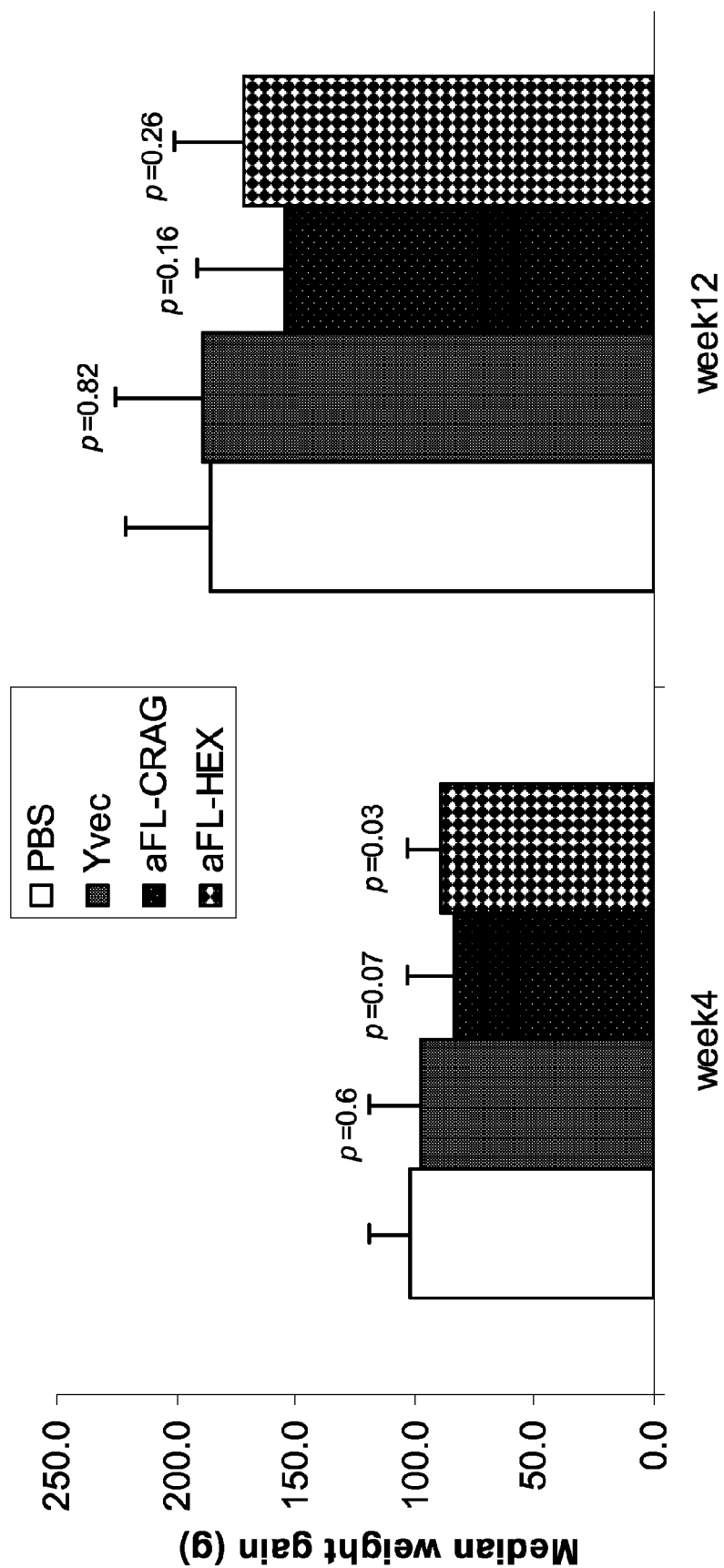


Fig. 13

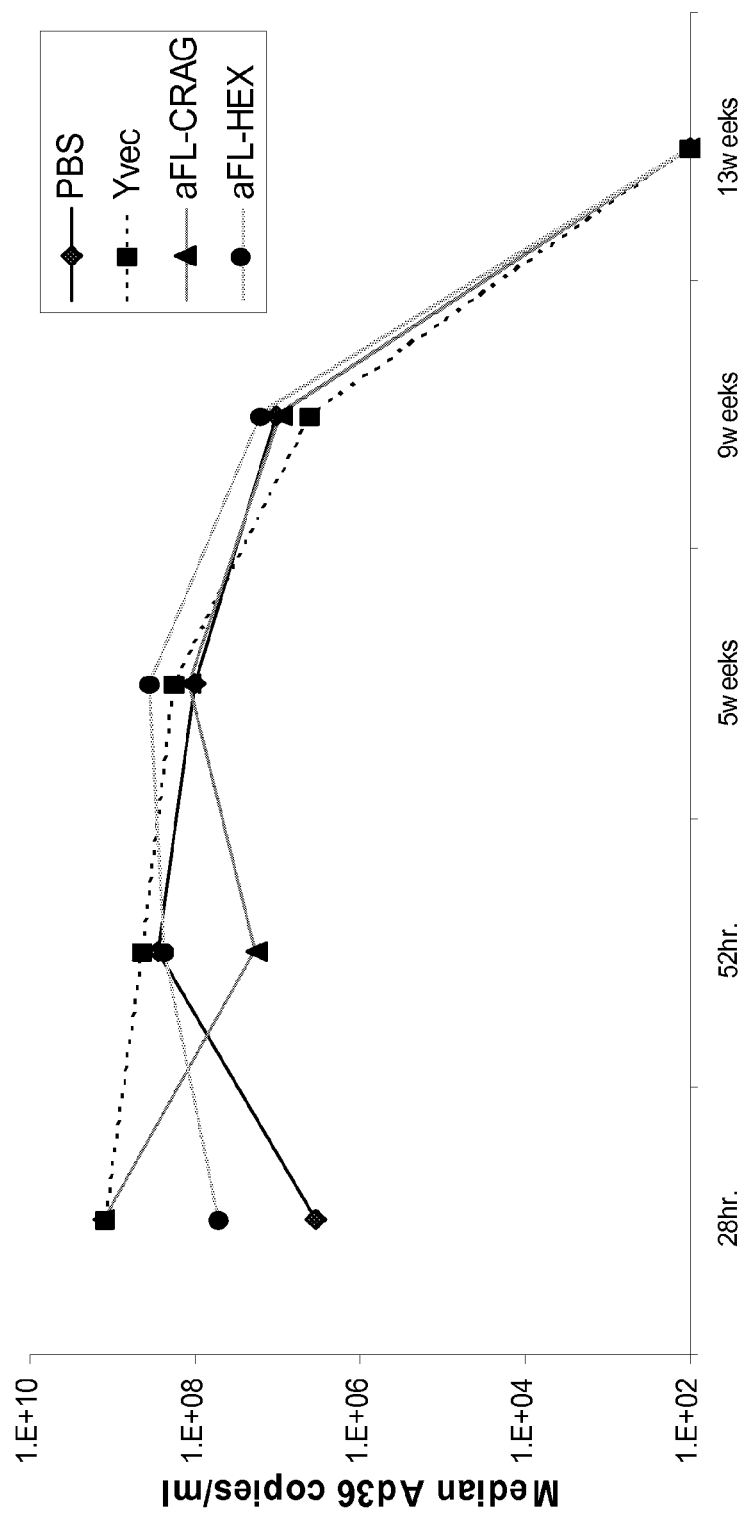


Fig. 14

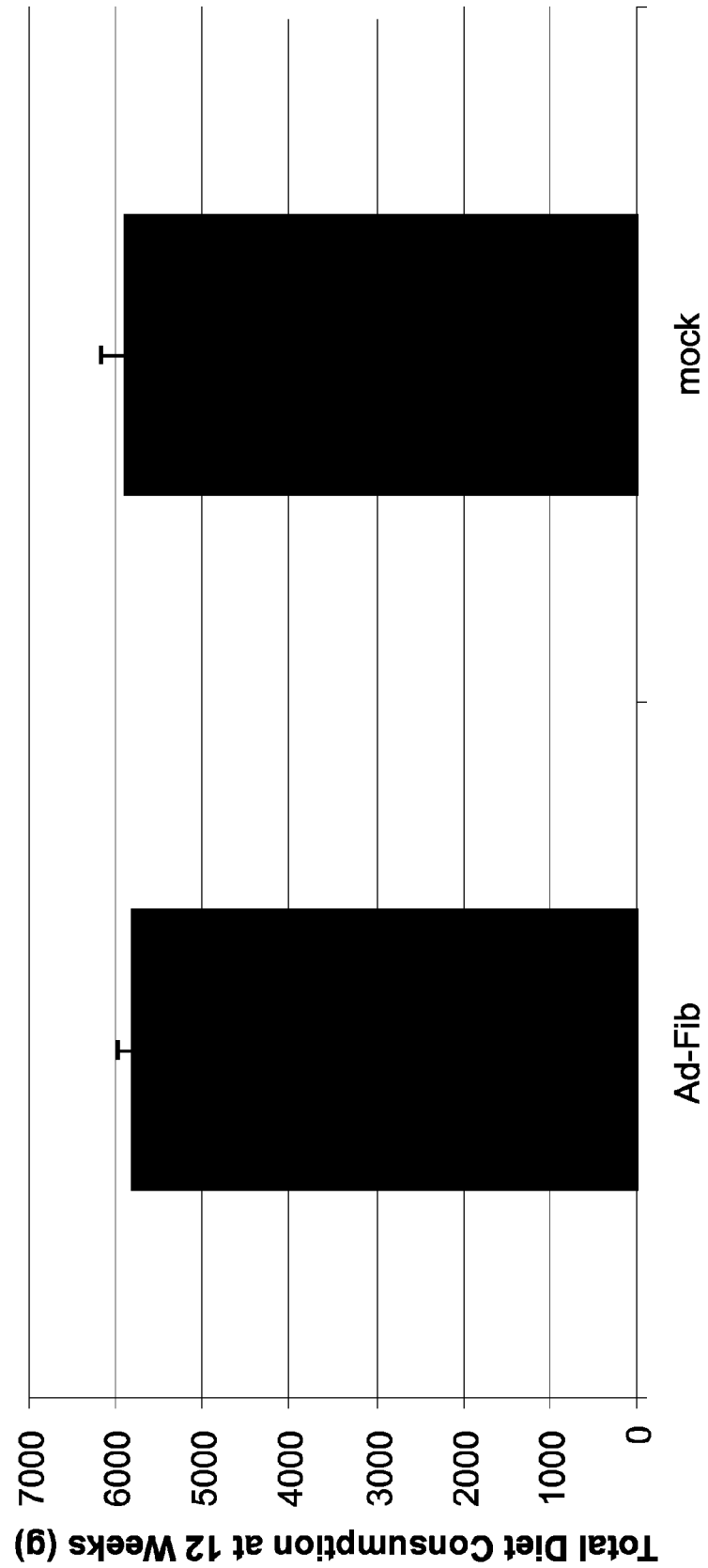


Fig. 15

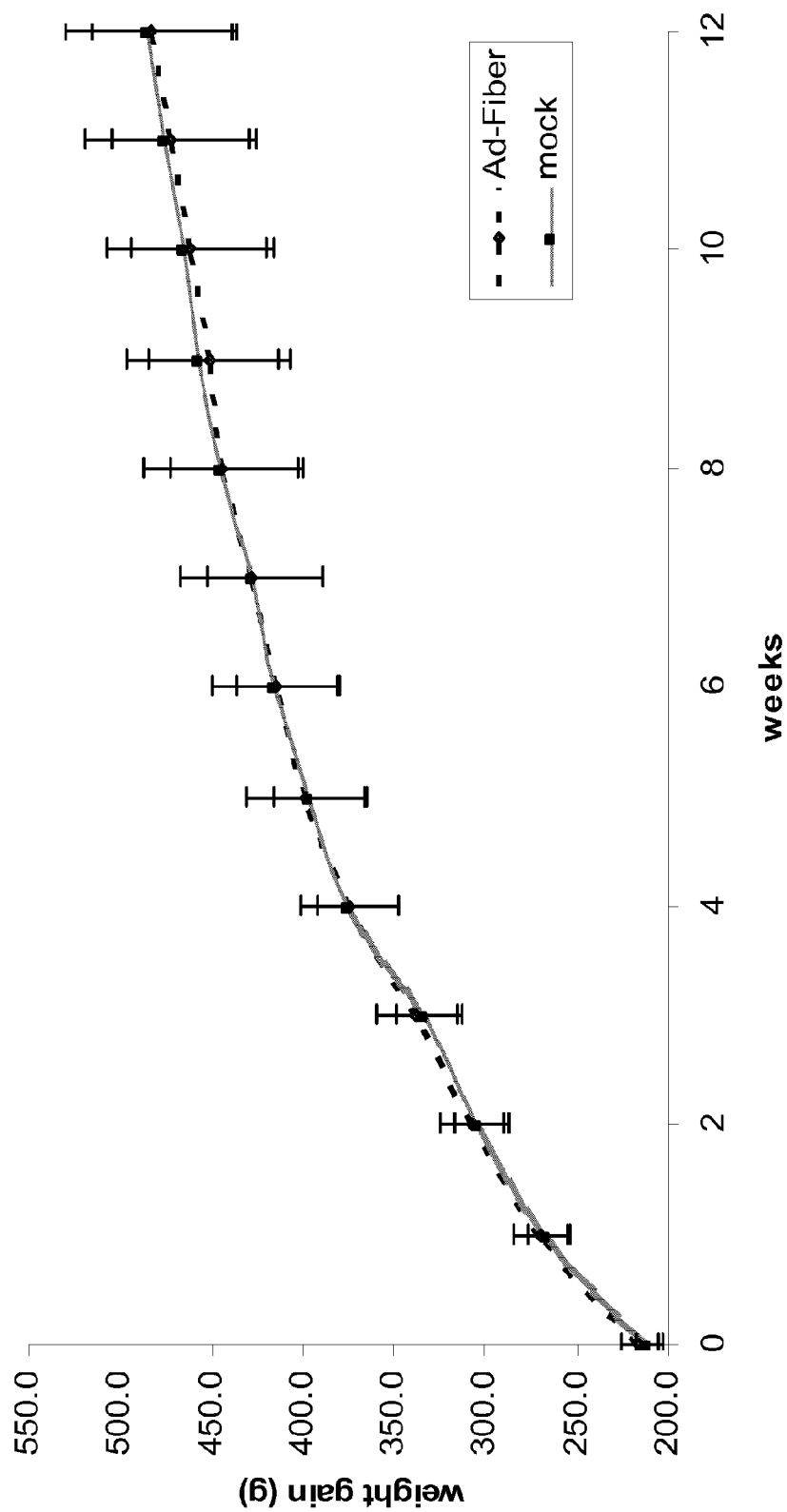
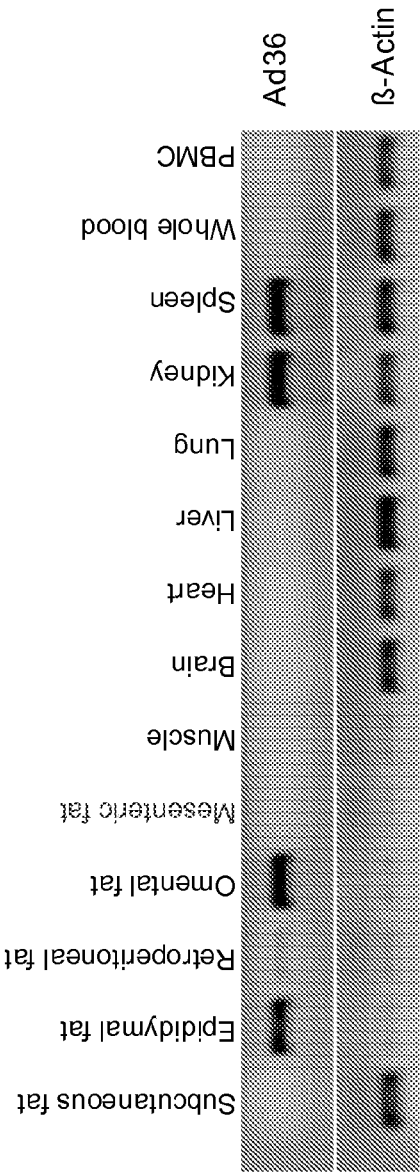


Fig. 16



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COMPOSITIONS AND METHODS FOR THE TREATMENT OR PREVENTION OF HUMAN ADENOVIRUS-36 INFECTION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a national stage application under 35 U.S.C. 371 of PCT Application No. PCT/US2011/65868, having an international filing date of Dec. 19, 2011, which designated the United States, which PCT application claims the benefit of priority under 35 U.S.C. §119(e) from U.S. Provisional Application No. 61/424,472, filed Dec. 17, 2010, the entire disclosure of which is hereby incorporated by reference.

REFERENCE TO A SEQUENCE LISTING

This application contains a Sequence Listing submitted electronically as a text file by EFS-Web. The text file, named “3923-33-PCT_ST25”, has a size in bytes of 211 KB, and was recorded on 16 Dec. 2011. The information contained in the text file is incorporated herein by reference in its entirety pursuant to 37 CFR §1.52(e)(5).

FIELD OF THE INVENTION

The present invention generally relates to immunotherapeutic compositions and methods for the prevention and/or treatment of human adenovirus-36 infection, as well as the prevention and/or treatment of obesity and/or obesity-associated disorders or other sequela related to human adenovirus-36 infection.

BACKGROUND OF THE INVENTION

The terms “obesity” and “overweight” or “pre-obese” define ranges of weights that are greater than weights that are generally considered to be healthy for a person of a given height. According to a report in August 2010 by the Centers for Disease Control (CDC), “no state met the *Healthy people* 2010 obesity target of 15%, and the self-reported prevalence of obesity among U.S. adults had increased 1.1 percentage points from 2007” (Sherry et al., *Morbidity and Mortality Weekly Report* (MMWR), 59; 1-5; Aug. 3, 2010). In children and teens, excess weight represents a very serious health issue. The 2007-2008 National Health and Nutrition Examination Survey (NHANES) estimated that 17% of individuals age 2-19 are obese (CDC). Indeed, the CDC and the WHO have referred to an “obesity epidemic” in many populations worldwide. Overweight and obese individuals have a higher likelihood of developing a variety of health problems including, but not limited to, cardiovascular diseases and associated conditions (e.g., high blood pressure, high cholesterol), type 2 diabetes, respiratory disorders, cancer, reproductive disorders, hepatic dysfunction, and osteoarthritis.

Several different factors can contribute to obesity or being overweight, and the condition can be a complex health issue for many individuals. Behavioral factors, environmental factors, genetics, illness, and/or infectious agents may play a role in the condition. Lack of sufficient physical activity and excess calorie intake in the diet, i.e., caloric imbalance, are the most apparent and common causes of being overweight or obese. However, there appear to be several genetic factors that may predispose certain individuals to weight gain, including mutations in genes related to control of feeding behavior, and various genetic mutations or correlations of genotype with

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obesity in individuals and populations. In addition to these factors, various illnesses and drugs can also impact an individual's weight. More recently, infectious agents have been identified as contributing to some cases of obesity.

A few infectious agents have been associated with obesity in non-human animals, and one in particular has been associated with human obesity. Human adenovirus-36 (also denoted Ad-36, Adv-36, or hAdv-36) was first described in a child with diabetes in 1980 (Wigand et al., 1980, *Arch. Virol.* 64(3):225-233). Beginning in the early 1990's, experiments by Dhurandhar and colleagues first showed that Ad-36 increased adiposity in chickens and in mice ((Dhurandhar et al., 1990, *J. Bombay Vet. College* 2:131-132; Dhurandhar et al., 1992, *Vet. Microbiol.*, 31:101-107; Dhurandhar et al., 2000, *Int J Obes Relat Metab Disord* 24:989-996; Dhurandhar et al., 2001, *Int. J. Obes. Relat. Metab. Disord.* 25(7):990-996), as well as in monkeys (Dhurandhar, et al., 2002, *J. Nutr.* 132(10):3155-3160). In mice and chickens, infection with Ad-36 resulted in viremia, infection of adipose tissue, increased visceral fat, total body fat, and/or body weight, and reduced serum cholesterol and triglycerides. In monkeys, Ad-36 promoted weight gain and lowered serum cholesterol. Pasarica and colleagues have shown that human Ad-36 induces adiposity, increases insulin sensitivity, and alters hypothalamic monoamines in rats (Pasarica et al., 2006, *Obesity* 14(11):1905-1913).

In humans, Ad-36 has been shown to have a high probability of being associated with obesity, where a unique phenotype of low serum cholesterol and triglyceride levels was present in about 30% of obese humans subjects having anti-Ad-36 antibodies, whereas only 5% of the non-obese humans tested had antibodies to Ad-36 (Dhurandhar et al., 1997, *FASEB J.* 3:A230; Atkinson et al., 1998, *Int J Obes Relat Metab Disord* 22(Suppl): S57). An epidemiological study showed that 30% of obese people were infected with Ad-36 compared to only 11% of lean people in the study (Atkinson et al., 2005, *Int J Obes* (Lond), 29(3):281-286). These investigators showed that Ad-36 is associated with increased body weight and the reduction of serum lipids in humans. Additional researchers have reported an association between human Ad-36 and lipid disorders or obesity rates in children and adolescents worldwide (Na et al., 2010, *Int. J. Obes.* 34:89-93; Gabbert et al., 2010, *Pediatrics* 2010; 126:721-726; and Atkinson et al., 2010, *Int. J. Ped. Obes.* 5:157-160). Further work by Pasarica and Dhurandhar and colleagues showed that Ad-36 induces commitment, differentiation, and lipid accumulation in human adipose-derived stem cells (Pasarica et al., 2008, *Stem Cells* 26:969-978). Moreover, in vitro adipogenesis was shown to be accelerated by infection of preadipocytes with human Ad-36 (Vangipuram et al., 2004, *Obes. Res.* 12(5):770-777), and infection was also shown to increase insulin sensitivity and suppress the expression of leptin mRNA (Vangipuram et al., 2007, *Int. J. Obes.* (Lond.) 31(1):87-96. The activity of the E4 orf1 gene of Ad-36 has been suggested to be responsible for this adipogenesis (Rogers et al., 2008, *International Journal of Obesity* 32:397-406).

In 2010, Arnold and colleagues reported the complete characterization of the human Ad-36 genome (Arnold et al., 2010, *Virus Res.* 149:152-161). Diagnostic assays have been described for the identification of Ad-36 infection in human tissues, via identification or use of anti-Ad-36 antibodies (see, e.g., WO 98/44946, WO 2007/120362), and a diagnostic test for Ad-36 is in commercial development (Scandivir AB). However, a treatment for the viral infection, once identified, is lacking; no preventative or therapeutic treatment that directly targets Ad-36 infection is currently commercially available. Accordingly, there remains a need in the art for an effective

prophylactic and/or therapeutic treatment for adenovirus-36 infection, in order to reduce or eliminate Ad-36-associated obesity and overweight conditions.

SUMMARY OF THE INVENTION

One embodiment of the invention relates to an immunotherapeutic composition comprising: (a) a yeast vehicle; and (b) an adenovirus-36 (Ad-36) antigen comprising one or more Ad-36 proteins and/or immunogenic domains of such proteins. In one aspect, the Ad-36 proteins include at least one protein selected from, but is not limited to: hexon, fiber, CR1 α , and CR1 γ , and/or at least one immunogenic domain of at least one of the proteins. In one aspect, the Ad-36 proteins include at least one immunogenic domain of CR1 α and at least one immunogenic domain of CR1 γ .

In one aspect, the Ad-36 antigen comprises Ad-36 sequences, wherein the Ad-36 sequences consist of: positions 71-136 of Ad-36 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain; positions 145-169 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain; positions 290-313 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain; and positions 334-363 of Ad-36 SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain. For example, such an Ad-36 antigen can include, but is not limited to, an amino acid sequence selected from the group consisting of: SEQ ID NO:42 or a corresponding sequence from another Ad-36 strain, SEQ ID NO:48 or a corresponding sequence from another Ad-36 strain and SEQ ID NO:49 or a corresponding sequence from another Ad-36 strain.

In one aspect, the Ad-36 antigen comprises Ad-36 sequences, wherein the Ad-36 sequences consist of: positions 136-218 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain; positions 235-285 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain; positions 297-308 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain; and positions 410-450 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain. For example, such an Ad-36 antigen can include, but is not limited to, SEQ ID NO:43 or a corresponding sequence from another Ad-36 strain, SEQ ID NO:50 or a corresponding sequence from another Ad-36 strain and SEQ ID NO:51 or a corresponding sequence from another Ad-36 strain.

In another aspect, the Ad-36 antigen comprises Ad-36 sequences, wherein the Ad-36 sequences consist of positions 2-944 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain. For example, such an Ad-36 antigen can include, but is not limited to, SEQ ID NO:44 or a corresponding sequence from another Ad-36 strain, SEQ ID NO:52 or a corresponding sequence from another Ad-36 strain and SEQ ID NO:53 or a corresponding sequence from another Ad-36 strain.

In yet another aspect, the Ad-36 antigen comprises Ad-36 sequences, wherein the Ad-36 sequences consist of: positions 71-136 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain; positions 145-169 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain; positions 290-313 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain; positions 334-363 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain; positions 136-218 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain; positions 235-285 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain; positions 297-308 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain; and positions 410-450 of SEQ ID NO:18 or a corresponding sequence

from another Ad-36 strain. For example, such an Ad-36 antigen can include, but is not limited to, SEQ ID NO: 45 or a corresponding sequence from another Ad-36 strain, and positions 7 to 418 of SEQ ID NO:45 or a corresponding sequence from another Ad-36 strain.

In another aspect, the Ad-36 antigen comprises Ad-36 sequences, wherein the Ad-36 sequences consist of: positions 136-218 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain; positions 235-285 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain; positions 297-308 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain; positions 410-450 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain; positions 71-136 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain; positions 145-169 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain; positions 290-313 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain; and positions 334-363 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain. For example, such an Ad-36 antigen can include, but is not limited to, SEQ ID NO:46 or a corresponding sequence from another Ad-36 strain, and positions 7 to 418 of SEQ ID NO:46 or a corresponding sequence from another Ad-36 strain.

In another aspect, the Ad-36 antigen comprises Ad-36 sequences, wherein the Ad-36 sequences consist of: positions 18-60 of SEQ ID NO:26 or a corresponding sequence from another Ad-36 strain; positions 123-157 SEQ ID NO:26 or a corresponding sequence from another Ad-36 strain; positions 19-60 of SEQ ID NO:29 or a corresponding sequence from another Ad-36 strain; and positions 83-116 of SEQ ID NO:29 or a corresponding sequence from another Ad-36 strain. For example, such an Ad-36 antigen can include, but is not limited to, SEQ ID NO:47 or a corresponding sequence from another Ad-36 strain, SEQ ID NO:54 or a corresponding sequence from another Ad-36 strain, and SEQ ID NO:55 or a corresponding sequence from another Ad-36 strain.

In any of the aspects or embodiments of the invention described above or elsewhere herein, in one aspect, the Ad-36 antigen is expressed by the yeast vehicle. In one aspect, the yeast vehicle is a whole yeast. In one aspect, the yeast is killed. In one aspect, the yeast is heat-inactivated. In one aspect, the yeast vehicle is from a genus selected from: *Saccharomyces*, *Candida*, *Cryptococcus*, *Hansenula*, *Kluyveromyces*, *Pichia*, *Rhodotorula*, *Schizosaccharomyces* and *Yarrowia*. In one aspect, the yeast vehicle is from *Saccharomyces*. In one aspect, the yeast vehicle is from *Saccharomyces cerevisiae*.

In any of the aspects or embodiments of the invention described above or elsewhere herein, in one aspect, a composition of the invention is formulated in a pharmaceutically acceptable excipient suitable for administration to an individual.

Another embodiment of the invention relates to a fusion protein comprising two or more Ad-36 proteins and/or immunogenic domains of one or more Ad-36 proteins, wherein the Ad-36 proteins include at least one protein selected from: hexon, fiber, CR1 α , and CR1 γ , and/or at least one immunogenic domain of at least one of the proteins. In one aspect, the Ad-36 proteins include E4 or at least one immunogenic domain thereof. In one aspect, the Ad-36 proteins include at least one immunogenic domain of CR1 α and at least one immunogenic domain of CR1 γ . In one aspect, the fusion protein comprises: (a) Ad-36 sequences consisting of: positions 71-136 of Ad-36 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain; positions 145-169 of SEQ ID NO:34 or a corresponding sequence from another

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Ad-36 strain; positions 290-313 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain; and positions 334-363 of Ad-36 SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain; (b) Ad-36 sequences consisting of: positions 136-218 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain; positions 235-285 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain; positions 297-308 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain; and positions 410-450 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain; (c) Ad-36 sequences consisting of: positions 2-944 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain; (d) Ad-36 sequences consisting of: positions 71-136 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain; positions 145-169 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain; positions 290-313 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain; positions 334-363 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain; positions 136-218 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain; positions 235-285 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain; positions 297-308 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain; and positions 410-450 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain; (e) Ad-36 sequences consisting of: positions 136-218 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain; positions 235-285 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain; positions 297-308 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain; positions 410-450 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain; positions 71-136 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain; positions 145-169 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain; positions 290-313 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain; and positions 334-363 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain; or (f) Ad-36 sequences consisting of: positions 18-60 of SEQ ID NO:26 or a corresponding sequence from another Ad-36 strain; positions 123-157 SEQ ID NO:26 or a corresponding sequence from another Ad-36 strain; positions 19-60 of SEQ ID NO:29 or a corresponding sequence from another Ad-36 strain; and positions 83-116 of SEQ ID NO:29 or a corresponding sequence from another Ad-36 strain. In one aspect, the fusion protein is selected from the group of: SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, and SEQ ID NO:55.

Yet another embodiment of the invention relates to a recombinant nucleic acid molecule encoding any of the fusion proteins described above or elsewhere herein.

Another embodiment of the invention relates to an isolated cell transfected with the recombinant nucleic acid molecule above. In one aspect, the cell is a yeast cell.

Further embodiments of the invention relate to a composition comprising any of the fusion proteins, recombinant nucleic acid molecules, or isolated cells, described above or elsewhere herein. In any of these embodiments, in one aspect, the composition further comprises at least one biological response modifier.

Another embodiment of the invention relates to a method to treat adenovirus-36 (Ad-36) infection in a subject. The method includes the step of administering to a subject that has

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been infected with Ad-36 any of the compositions described above or elsewhere herein, wherein administration of the composition to the subject reduces Ad-36 infection in the subject. In one aspect, administration of the composition to the subject reduces Ad-36 viral load in the subject.

Yet another embodiment of the invention relates to a method to treat adenovirus-36 (Ad-36) infection in a subject. The method includes the step of administering to a subject that has been infected with Ad-36 any of the compositions described above or elsewhere herein, wherein administration of the composition to the subject reduces the rate of weight gain in the subject.

Another embodiment of the invention relates to a method to treat adenovirus-36 (Ad-36)-associated obesity or excess weight in a subject. The method includes the step of administering to a subject that has been infected with Ad-36 and has a body mass index (BMI) of at least 25, any of the compositions described above or elsewhere herein, wherein administration of the composition to the subject reduces the BMI in the subject.

Yet another embodiment of the invention relates to a method to treat adenovirus-36 (Ad-36)-associated obesity or excess weight in a subject. The method includes the step of administering to a subject that has been infected with Ad-36 and has a body mass index (BMI) of less than 25, any of the compositions described above or elsewhere herein, wherein administration of the composition to the subject reduces the BMI in the subject or reduces the rate of weight gain in the subject.

Another embodiment of the invention relates to a method to elicit an antigen-specific, T cell-mediated immune response against an Ad-36 antigen. The method includes the step of administering to a subject any of the compositions described above or elsewhere herein.

Yet another embodiment of the invention relates to a method to prevent Ad-36 infection in a subject or to reduce the rate of weight gain in a subject. The method includes the step of administering to a subject that has not been infected with Ad-36 any of the compositions described above or elsewhere herein. In one aspect, the subject has a BMI of less than 25. In one aspect, the subject has a BMI of 25 or greater. In one aspect, the subject is between age 2 and age 19. In one aspect, the subject is an adult.

Another embodiment of the invention relates to a method to immunize a population of individuals against Ad-36 infection, comprising administering to the population of individuals any of the compositions described above or elsewhere herein. In one aspect, the individuals are adults. In one aspect, the individuals are age 2 to 19. In one aspect, the individuals have a BMI of 25 or greater. In one aspect, the individuals have a BMI of less than 25.

Another embodiment of the invention relates to any of the compositions described above or elsewhere herein for use to treat Ad-36 infection.

Yet another embodiment of the invention relates to any of the compositions described above or elsewhere herein for use to prevent Ad-36 infection.

Another embodiment of the invention relates to any of the compositions described above or elsewhere herein for use to reduce the rate of weight gain in an individual infected with Ad-36.

Another embodiment of the invention relates to any of the compositions described above or elsewhere herein for use to elicit an Ad-36 immune response in an individual.

Yet another embodiment of the invention relates to the use of any of the compositions described above or elsewhere herein in the preparation of a medicament to treat Ad-36 infection.

Another embodiment of the invention relates to the use of any of the compositions described above or elsewhere herein in the preparation of a medicament to prevent Ad-36 infection.

Another embodiment of the invention relates to the use of any of the compositions described above or elsewhere herein in the preparation of a medicament for reducing the rate of weight gain in an individual infected with Ad-36.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a digitized image of a western blot showing expression of: (1) a yeast-based immunotherapy composition expressing an Ad-36 fusion protein comprising fiber (FIB) (SEQ ID NO:42) under the control of a TEF2 promoter; (2) a yeast-based immunotherapy composition expressing an Ad-36 fusion protein comprising hexon (HEX) (SEQ ID NO:43) under the control of a TEF2 promoter; and (3) a yeast-based immunotherapy composition expressing an Ad-36 fusion protein comprising CR1 α and CR1 γ (CRAG) (SEQ ID NO:47) under the control of a TEF2 promoter.

FIG. 2 is a digitized image of a western blot showing expression of: (1) a yeast-based immunotherapy composition expressing an Ad-36 fusion protein comprising fiber (Ad-aFL-FIB) (SEQ ID NO:48) under the control of a Cup1 promoter; (2) a yeast-based immunotherapy composition expressing an Ad-36 fusion protein comprising hexon (Ad-aFL-HEX) (SEQ ID NO:50) under the control of a Cup1 promoter; (3) a yeast-based immunotherapy composition expressing an Ad-36 fusion protein comprising CR1 α and CR1 γ (Ad-aFL-CRAG) (SEQ ID NO:54) under the control of a Cup1 promoter; and (4) a yeast-based immunotherapy composition expressing an Ad-36 fusion protein comprising full length hexon (Ad-aFL-Hexon-Full) (SEQ ID NO:52) under the control of a TEF2 promoter.

FIG. 3 is a bar graph showing the expression of genes encoding Ad-36 E1A, Ad-36 E4orf1, and Ad-36 hexon in rat adipose-derived stem cells (ADS) 15 hours after Ad-36 infection in vitro.

FIG. 4 is a bar graph showing the expression of genes encoding Ad-36 E1A, Ad-36 E4orf1 and Ad-36 hexon in A549 cells (natural host cell for human adenoviruses) 15 hours after Ad-36 infection in vitro.

FIG. 5 is a graph showing the mock control for the early virus particles (V.P.) kinetics study.

FIG. 6 is a graph showing early virus particles (V.P.) kinetics after 10^7 PFU Ad-36 challenge.

FIG. 7 is a graph showing early virus particles (V.P.) kinetics after 10^8 PFU Ad-36 challenge.

FIG. 8 is a graph showing early virus particles (V.P.) kinetics after 10^9 PFU Ad-36 challenge.

FIG. 9 is a digitized image of nested PCR detecting Ad-36 DNA in visceral adipose tissue from rats two weeks after infection with various doses of the virus in vivo.

FIG. 10 is a scatter graph showing body weight gain 18 weeks after Ad-36 infection in rats which were injected with PBS (PBS), control yeast (YVEC), a yeast-based immunotherapy composition expressing a fusion protein comprising Ad-36 CR1 α and Ad-36 CR1 γ (aFL-Crag), and a yeast-based immunotherapy composition expressing a fusion protein comprising Ad-36 hexon (aFL-Hex).

FIG. 11 is a line graph plotting the time course of median body weight gain over baseline in Ad-36 infected rats which

were injected with PBS (PBS), control yeast (YVEC), a yeast-based immunotherapy composition expressing a fusion protein comprising Ad-36 CR1 α and Ad-36 CR1 γ (aFL-Crag), and a yeast-based immunotherapy composition expressing a fusion protein comprising Ad-36 hexon (aFL-Hex).

FIG. 12 is a bar graph comparing the median body weight gain at week 4 and week 12 after Ad-36 infection in rats which were injected with PBS (PBS, white bars), control yeast (YVEC, gray bars), a yeast-based immunotherapy composition expressing a fusion protein comprising Ad-36 CR1 α and Ad-36 CR1 γ (aFL-CRAG, black bars), and a yeast-based immunotherapy composition expressing a fusion protein comprising Ad-36 hexon (aFL-HEX, checkered bars).

FIG. 13 is a line graph showing the Ad-36 viral kinetics in the blood for rats that were infected with Ad-36 and injected with PBS (PBS), control yeast (YVEC), a yeast-based immunotherapy composition expressing a fusion protein comprising Ad-36 CR1 α and Ad-36 CR1 γ (aFL-Crag), and a yeast-based immunotherapy composition expressing a fusion protein comprising Ad-36 hexon (aFL-Hex).

FIG. 14 is a bar graph comparing the total diet consumption (by weight) over 12 weeks of non-Ad-36-infected rats injected with a yeast-based immunotherapeutic expressing an Ad-36 fiber protein and rats which were mock-injected (no immunotherapeutic).

FIG. 15 is a line graph comparing the weight gain over 12 weeks of non-Ad-36-infected rats injected with a yeast-based immunotherapeutic expressing an Ad-36 fiber protein and rats which were mock-injected (no immunotherapeutic).

FIG. 16 is a digitized image of PCR showing Ad-36 DNA in organs and tissues of a rat 15 weeks after intraperitoneal inoculation with the Ad-36 virus.

DETAILED DESCRIPTION OF THE INVENTION

This invention generally relates to immunotherapeutic compositions and methods for the prevention and/or treatment of adenovirus-36 (Ad-36) infection, as well as the prevention and/or treatment of obesity, obesity-associated disorders related to adenovirus-36 infection, and adipose tissue hypertrophy related to Ad-36 infection. The invention includes a yeast-based immunotherapeutic composition (also referred to as yeast-based immunotherapy) comprising a yeast vehicle and Ad-36 antigen(s) that have been designed to elicit a prophylactic and/or therapeutic immune response against Ad-36 infection in a subject. The invention includes the use of such compositions to prevent and/or treat Ad-36 infection. The invention also includes the recombinant nucleic acid molecules used in the yeast-based compositions of the invention, as well as the proteins encoded thereby, for use in any immunotherapeutic composition and/or therapeutic protocol for Ad-36 infection.

The yeast-based, Ad-36-specific immunotherapeutic compositions of the invention induce innate immune responses, as well as adaptive immune responses that specifically target Ad-36, including CD4-dependent TH17 and TH1 T cell responses and antigen-specific CD8 $^+$ T cell responses, which include cytotoxic T lymphocyte (CTL) responses. In addition, yeast-based, Ad-36-specific immunotherapeutic compositions of the invention modulate regulatory T cell (Treg) numbers and/or functionality. The breadth of the immune response elicited by Ad-36-specific yeast-based immunotherapy can be modulated toward the desired type of immune response (e.g., TH1 versus TH17 versus Treg), and is well-suited to target Ad-36. In contrast to vaccines that immunize by generating neutralizing antibody responses, yeast-based

immunotherapeutic compositions targeting Ad-36 elicit antigen-specific, broad-based, and potent cellular immune responses, including CD4⁺ T cell responses that are believed to be particularly effective in providing immunity against adenoviruses, since early adenovirus infection may inhibit MHC class I expression. The ability of yeast-based immunotherapy to enhance TH17 T cell responses is also believed to be useful, since IL-17 blocks differentiation of precursor fat cells into bonafide adipocytes and also promotes lipolysis (Shin et al., 2009).

Yeast-based immunotherapy is also highly adept at activating antigen presenting cells, and has a unique ability to cross-prime the immune response, generating CD8⁺ CTL responses that are typically effective against viral infections, even in the face of what may otherwise be a suppressive environment. Yeast-based immunotherapy can be designed to target regions of Ad-36 that are specific to this virus, or to target regions that are conserved among many adenovirus serotypes and/or to target a mixture of these regions, making the vaccine highly adaptable to the needs of the infected individual, and to target both protective and therapeutic immunity. Since this type of immunotherapy utilizes the natural ability of the antigen presenting cell to present relevant immunogens, it is not necessary to know the precise identity of CTL epitopes or MHC Class II epitopes to produce an effective immunotherapeutic and indeed, multiple CD4 and CD8 T cell epitopes can be targeted in a single composition. Therefore, yeast-based Ad-36 immunotherapy, by activating both the innate and the adaptive immune response, is expected to effectively target Ad-36-infected cells for non-cytopathic clearance, destruction, or both. In addition to being effective in treating excess weight or controlling the rate of weight gain, as well as in treating conditions related to excess weight or weight gain that are associated with Ad-36 infection, the yeast-based immunotherapeutic compositions of the invention are expected to be effective in cases where adipose tissue displays abnormal growth or hypertrophy that is associated with the presence of Ad-36, such as occurs in patients infected with HIV. Indeed, prior to development of full-blown AIDS, HIV-infected patients and patients experiencing Ad-36-associated abnormal adiposity that may develop in the context of reduced or impaired normal immune function, administration of the yeast-based immunotherapy described herein may be effective to treat such patients by providing a broad-based immune response sufficient to reduce Ad-36 viral load and thereby resolve the abnormal adipose tissue hypertrophy. Yeast-based immunotherapy activates multiple pathways of the immune system, and is expected to be effective where other therapeutic approaches, including other immunotherapeutic approaches, lack efficacy.

The compositions, methods and uses of the invention are directed to the prevention and/or treatment of Ad-36 infection, which may reduce or prevent one or more symptoms or conditions associated with Ad-36 infection, including but not limited to, obesity, being overweight, undesirable or abnormal weight gain, and/or abnormal adipose tissue hypertrophy. By addressing these conditions, downstream sequela of obesity and being clinically overweight, or conditions associated with obesity, excess weight, undesirable or abnormal weight gain, or abnormal adipose tissue hypertrophy, may also be reduced. Such conditions include, but are not limited to, high serum cholesterol, high triglycerides, high blood pressure, respiratory conditions, insulin resistance, and type II diabetes.

Compositions of the Invention

One embodiment of the present invention relates to a yeast-based immunotherapy composition which can be used to prevent and/or treat Ad-36 infection or to alleviate at least one symptom resulting from the Ad-36 infection, including but not limited to, obesity, being overweight, undesired or abnormal weight gain, or the propensity therefore. The composition comprises: (a) a yeast vehicle; and (b) one or more Ad-36 protein(s) and/or immunogenic domain(s) thereof (collectively, "Ad-36 antigens"). In conjunction with the yeast vehicle, the Ad-36 proteins are most typically expressed as recombinant proteins by the yeast vehicle (e.g., by an intact yeast or yeast spheroplast, which can optionally be further processed to a yeast cytoplasm, yeast ghost, or yeast membrane extract or fraction thereof), although it is an embodiment of the invention that one or more such Ad-36 proteins are loaded into a yeast vehicle or otherwise complexed with, attached to, mixed with or administered with a yeast vehicle as described herein to form a composition of the present invention. According to the present invention, reference to a "heterologous" protein or "heterologous" antigen, including a heterologous fusion protein, in connection with a yeast vehicle of the invention, means that the protein or antigen is not a protein or antigen that is naturally expressed by the yeast, although a fusion protein may include yeast sequences or proteins or portions thereof that are also naturally expressed by yeast. Ad-36 proteins are heterologous with respect to yeast. Target antigens useful in the present invention are typically Ad-36 proteins and/or immunogenic domains thereof.

Another embodiment of the invention relates to novel Ad-36 fusion proteins described herein. In one aspect, such Ad-36 fusion proteins are useful in an immunotherapeutic composition of the invention, including a yeast-based immunotherapeutic composition of the invention. Such fusion proteins, and/or the recombinant nucleic acid molecules encoding such proteins, can also be used in, in combination with, or to produce, a non-yeast-based immunotherapeutic composition, which may include, without limitation, a DNA vaccine, a protein subunit vaccine, a recombinant viral-based immunotherapeutic composition, and a killed or inactivated pathogen vaccine. In another embodiment, such fusion proteins can be used in a diagnostic assay for Ad-36 and/or to generate antibodies against Ad-36. Described herein are exemplary Ad-36 fusion proteins providing selected portions of Ad-36 which are particularly useful in yeast-based immunotherapeutic compositions of the invention.

Adenovirus-36

Adenovirus-36 (also referred to herein as Ad-36, Adv-36, hAdv-36, or HAdV-D36, or adenovirus serotype 36, all of which may be used interchangeably) is one of 52 currently known serotypes of adenoviruses that infect humans, from the Family Adenoviridae, Genus *Mastadenovirus*, Species *Human Adenovirus D* (HAdV-D). The virus was first identified in a child with diabetes and enteritis (Wigand et al., 1980, supra) and was deposited with the ATCC as ATCC® Number VR-1610TH by Wigand. In 2010, Arnold and colleagues sequenced the complete Ad-36 genome (Arnold et al., 2010, supra), which is deposited under GenBank® Accession No. GQ384080.1 (GI:261875889). The nucleotide sequence of this representative adenovirus-36 genomic sequence is represented herein by SEQ ID NO:1.

Ad-36 is a double-stranded DNA virus with a 35,152 bp genome, organized into 39 predicted open reading frames (ORFs). The coding sequences that are most divergent from other adenoviruses are found in the hexon, CR1 β , CR1 γ , and fiber coding regions. Table 1 indicates the individual protein sequences encoded by the Ad-36 genome (SEQ ID NO:1). It is noted that small variations may occur in the amino acid

sequence between different viral isolates of the same protein from Ad-36. However, using the guidance provided herein and the reference to the exemplary Ad-36 sequences, one of skill in the art will readily be able to produce a variety of Ad-36-based proteins, including fusion proteins, from any Ad-36 strain (isolate) or genotype, for use in the compositions and methods of the present invention, and as such, the invention is not limited to the specific sequences disclosed herein. Reference to an Ad-36 protein or antigen anywhere in this disclosure, or to any functional, structural, or immunogenic domain thereof, can accordingly be made by reference to a particular sequence from one or more of the sequences presented in this disclosure, or by reference to the same, similar or corresponding sequence from a different Ad-36 isolate (strain). One of skill in the art will readily be able to identify the position of the corresponding sequence for each protein in Table 1 in a given Ad-36 sequence of any Ad-36 strain/isolate, given the guidance provided below, even though some amino acids may differ from those sequences in Table 1.

TABLE 1

Adenovirus-36 Protein Sequences	
Protein Name	Sequence Identifier
E1A 28K	SEQ ID NO: 2
E1A 21K	SEQ ID NO: 3
E1B 19K	SEQ ID NO: 4
E1B 55K	SEQ ID NO: 5
pIX	SEQ ID NO: 6
IVa2	SEQ ID NO: 7
Pol protein	SEQ ID NO: 8
13.6K	SEQ ID NO: 9
pTP	SEQ ID NO: 10
52K	SEQ ID NO: 11
pIIIa	SEQ ID NO: 12
III	SEQ ID NO: 13
pVII	SEQ ID NO: 14
V	SEQ ID NO: 15
pX	SEQ ID NO: 16
pVI	SEQ ID NO: 17
Hexon	SEQ ID NO: 18
Protease	SEQ ID NO: 19
DBP	SEQ ID NO: 20
100K	SEQ ID NO: 21
33K	SEQ ID NO: 22
22K	SEQ ID NO: 23
pVIII	SEQ ID NO: 24
E3 12.5K	SEQ ID NO: 25
E3 CR1 α	SEQ ID NO: 26
E3 18.4K	SEQ ID NO: 27
E3 50K (CR1 β)	SEQ ID NO: 28
E3B1-2 30.8K (CR1 γ)	SEQ ID NO: 29
E3B2-2 10K (RID α)	SEQ ID NO: 30
E3B2-2 14.6K (RID β)	SEQ ID NO: 31
E3B 14.7K	SEQ ID NO: 32
U protein	SEQ ID NO: 33
Fiber	SEQ ID NO: 34
E4 ORF 6/7	SEQ ID NO: 35
E4 34K	SEQ ID NO: 36
E4 17K	SEQ ID NO: 37
E4 ORF4	SEQ ID NO: 38
E4 ORF3	SEQ ID NO: 39
E4 ORF2	SEQ ID NO: 40
E4 ORF1	SEQ ID NO: 41

Adenovirus-36 Target Antigens and Constructs.

One embodiment of the invention relates to novel Ad-36 proteins and fusion proteins which can be used as target antigens in an immunotherapeutic composition of the invention, and recombinant nucleic acid molecules encoding these proteins or antigens. Described herein are several different novel Ad-36 proteins and fusion proteins for use as target antigens in a yeast-based immunotherapeutic composition or

other composition (e.g., other immunotherapeutic or diagnostic composition) that provide one, two, or multiple (three, four, five, six, seven, eight, nine, ten, or more) proteins and/or one, two or multiple immunogenic domains from one or more proteins, all contained within the same polypeptide and encoded by the same recombinant nucleic acid construct. The proteins used in the compositions of the invention include at least one Ad-36 antigen for immunizing an animal (prophylactically or therapeutically). The composition can include, one, two, a few, several or a plurality of Ad-36 antigens, including one or more immunogenic domains of one or more Ad-36 proteins, as desired.

According to the present invention, the general use herein of the term "antigen" refers: to any portion of a protein (peptide, partial protein, full-length protein), wherein the protein is naturally occurring or synthetically derived, to a cellular composition (whole cell, cell lysate or disrupted cells), to an organism (whole organism, lysate or disrupted cells) or to a carbohydrate, or other molecule, or a portion thereof. An antigen may elicit an antigen-specific immune response (e.g., a humoral and/or a cell-mediated immune response) against the same or similar antigens that are encountered by an element of the immune system (e.g., T cells, antibodies).

An antigen can be as small as a single epitope, or larger, and can include multiple epitopes. As such, the size of an antigen can be as small as about 5-12 amino acids (i.e., a peptide) and as large as: a full length protein, a multimer, a fusion protein, a chimeric protein, a whole cell, a whole microorganism, or any portions thereof (e.g., lysates of whole cells or extracts of microorganisms. In addition, antigens can include carbohydrates, which can be loaded into a yeast vehicle or into a composition of the invention. It will be appreciated that in some embodiments (i.e., when the antigen is expressed by the yeast vehicle from a recombinant nucleic acid molecule), the antigen is a protein, fusion protein, chimeric protein, or fragment thereof, rather than an entire cell or microorganism.

When the antigen is to be expressed in yeast, an antigen is of a minimum size capable of being expressed recombinantly in yeast, and is typically at least or greater than 25 amino acids in length, or at least or greater than 26, at least or greater than 27, at least or greater than 28, at least or greater than 29, at least or greater than 30, at least or greater than 31, at least or greater than 32, at least or greater than 33, at least or greater than 34, at least or greater than 35, at least or greater than 36, at least or greater than 37, at least or greater than 38, at least or greater than 39, at least or greater than 40, at least or greater than 41, at least or greater than 42, at least or greater than 43, at least or greater than 44, at least or greater than 45, at least or greater than 46, at least or greater than 47, at least or greater than 48, at least or greater than 49, or at least or greater than 50 amino acids in length, or is at least 25-50 amino acids in length, at least 30-50 amino acids in length, or at least 35-50 amino acids in length, or at least 40-50 amino acids in length, or at least 45-50 amino acids in length. Smaller proteins may be expressed, and considerably larger proteins (e.g., hundreds of amino acids in length or even a few thousand amino acids in length) may be expressed. In one aspect, a full-length protein or a structural or functional domain thereof or an immunogenic domain thereof that is lacking one or more amino acids from the N- and/or the C-terminus may be expressed (e.g., lacking between about 1 and about 20 amino acids from the N- and/or the C-terminus). Fusion proteins and chimeric proteins are also antigens that may be expressed in the invention. A "target antigen" is an antigen that is specifically targeted by an immunotherapeutic composition of the invention (i.e., an antigen against which elicitation of an immune response is desired). An "Ad-36 antigen" is an anti-

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gen derived, designed, or produced from one or more Ad-36 proteins such that targeting the antigen also targets Adenovirus-36.

When referring to stimulation of an immune response, the term “immunogen” is a subset of the term “antigen”, and therefore, in some instances, can be used interchangeably with the term “antigen”. An immunogen, as used herein, describes an antigen which elicits a humoral and/or cell-mediated immune response (i.e., is immunogenic), such that administration of the immunogen to an individual mounts an antigen-specific immune response against the same or similar antigens that are encountered by the immune system of the individual. In one embodiment, the immunogen elicits a cell-mediated immune response, including a CD4⁺ T cell response (TH1 and/or TH17) and/or a CD8⁺ T cell response (e.g., a CTL response).

An “immunogenic domain” of a given antigen can be any portion, fragment or epitope of an antigen (e.g., a peptide fragment or subunit or an antibody epitope or other conformational epitope) that contains at least one epitope that can act as an immunogen when administered to an animal. Therefore, an immunogenic domain is larger than a single amino acid and is at least of a size sufficient to contain at least one epitope. For example, a single protein can contain multiple different immunogenic domains. Immunogenic domains need not be linear sequences within a protein, such as in the case of a humoral immune response, where conformational domains are contemplated.

An epitope is defined herein as a single immunogenic site within a given antigen that is sufficient to elicit an immune response when provided to the immune system in the context of appropriate costimulatory signals and/or activated cells of the immune system. In other words, an epitope is the part of an antigen that is recognized by components of the immune system, and may also be referred to as an antigenic determinant. Those of skill in the art will recognize that T cell epitopes are different in size and composition from B cell or antibody epitopes, and that epitopes presented through the Class I MHC pathway differ in size and structural attributes from epitopes presented through the Class II MHC pathway. For example, T cell epitopes presented by Class I MHC molecules are typically between 8 and 11 amino acids in length, whereas epitopes presented by Class II MHC molecules are less restricted in length and may be up to 25 amino acids or longer. In addition, T cell epitopes have predicted structural characteristics depending on the specific MHC molecules bound by the epitope. Epitopes can be linear sequence epitopes or conformational epitopes (conserved binding regions). Most antibodies recognize conformational epitopes.

A “functional domain” of a given protein is a portion or functional unit of the protein that includes sequence or structure that is directly or indirectly responsible for at least one biological or chemical function associated with, ascribed to, or performed by the protein. For example, a functional domain can include an active site for enzymatic activity, a ligand binding site, a receptor binding site, a binding site for a molecule or moiety such as calcium, a phosphorylation site, or a transactivation domain.

A “structural domain” of a given protein is a portion of the protein or an element in the protein’s overall structure that has an identifiable structure (e.g., it may be a primary or tertiary structure belonging to and indicative of several proteins within a class or family of proteins), is self-stabilizing and/or may fold independently of the rest of the protein. A structural domain is frequently associated with or features prominently in the biological function of the protein to which it belongs.

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In some embodiments, an Ad-36 antigen useful in the present invention is a fusion protein. In one aspect of the invention, such a fusion protein can include two or more antigens. In one aspect, the fusion protein can include two or more immunogenic domains and/or two or more epitopes of one or more Ad-36 proteins. An immunotherapeutic composition containing such antigens may provide antigen-specific immunization in a broad range of patients. For example, a protein or fusion protein encompassed by the invention can include at least a portion or the full-length of any one or more Ad-36 proteins represented in Table 1 (amino acid sequences represented by SEQ ID NOs:2 through 41) and/or any one or more immunogenic domains of any one or more of these Ad-36 proteins, provided in any combination. In one embodiment, a protein useful in the present invention comprises one or more of the following Ad-36 proteins and/or one or more immunogenic domains of any one of more of the following proteins: hexon, fiber, CR1 α , CR1 γ , and/or E4. In one embodiment, an antigen useful in an immunotherapeutic composition of the invention is a single Ad-36 protein (full-length, near full-length, or portion thereof comprising at least, one, two, three, four or more immunogenic domains of a full-length protein). In one embodiment of the invention, an immunotherapeutic composition includes one, two, three, four, five or more individual yeast vehicles, each expressing or containing a different Ad-36 antigen.

In one embodiment of the invention, the Ad-36 antigen(s) for use in a composition or method of the invention is an Ad-36 antigen comprising or consisting of hexon, fiber, CR1 α , CR1 γ , and/or E4 and/or one or more domains (structural, functional or immunogenic) thereof, or any combination thereof. In one aspect, any one or more of these proteins or domains is full-length or near full-length. According to the present invention, reference to a “full-length” protein (or a full-length functional domain or full-length immunological domain) includes the full-length amino acid sequence of the protein or functional domain or immunological domain, as described herein or as otherwise known or described in a publicly available sequence. A protein or domain that is “near full-length”, which is also a type of homologue of a protein, differs from a full-length protein or domain, by the addition or deletion of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids from the N- and/or C-terminus of such a full-length protein or full-length domain. General reference to a protein or domain can include both full-length and near full-length proteins, as well as other homologues thereof. In one aspect, one or more of these proteins or domains comprise or consist of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more immunogenic domains. In one aspect, any one or more of these proteins or domains comprises at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the linear sequence of the corresponding full-length sequence or of a specified domain or portion of the full-length sequence. An N-terminal expression sequence and/or a C-terminal tag are optional for use with the Ad-36 antigens, and may be selected from several different sequences described elsewhere herein to improve expression, stability, and/or allow for identification and/or purification of the protein, or one or both of the N- or C-terminal sequences are omitted altogether. In addition, many different promoters suitable for use in yeast are known in the art. Furthermore if two or more Ad-36 proteins or domains thereof are included in an Ad-36 antigen, short intervening linker sequences (e.g., 1, 2, 3, 4, or 5, or larger, amino acid peptides) may optionally be introduced between portions of the protein or between the proteins and other elements (e.g., N-terminal peptides) for a variety of reasons, including the introduction of restriction enzyme sites to facilitate cloning and future manipulation of

the constructs. Finally, as discussed elsewhere herein, the sequences described herein are exemplary, and may be modified as described above to substitute, add, or delete sequences in order to accommodate preferences for Ad-36 strain or isolate, or consensus sequences and inclusion of preferred T cell epitopes, including dominant and/or subdominant T cell epitopes.

In one aspect of the invention, the Ad-36 antigens useful in the invention are antigens that are divergent, or less conserved, with respect to other adenoviruses (e.g., have relatively low sequence homology or identity with the same or equivalent proteins from other adenovirus serotypes/genotypes). In one embodiment of the invention, a divergent region of a protein, or reference to a protein or region of a protein that is divergent with respect to other proteins of similar structure and/or function (e.g., a region of an Ad-36 protein as compared to approximately the same or similar region of the same protein or an equivalent protein from another adenovirus serotype/genotype), is defined as a protein region for which there is less than about 60% average amino acid identity between the reference sequence and at least five other sequences from other sources that are equivalent in structure and or function, determined, for example, using a BLAST algorithm (described below). Accordingly, proteins or domains or portions of proteins from Ad-36 that are not highly conserved (are relatively or very non-conserved) with other adenovirus serotypes/genotypes are included in antigens and fusion proteins useful in the invention, in one embodiment of the invention. The inclusion of Ad-36 antigens that are divergent from other adenovirus antigens (e.g., similar or equivalent antigens, with respect to structure and/or function, from other adenovirus serotypes or genotypes) has the advantage of creating an immunotherapeutic composition that is specific for Ad-36 and potentially minimizes off-target effects of the immunotherapeutic or dilution of the specificity of the immunotherapeutic. In another aspect of the invention, antigens from conserved regions of Ad-36 (e.g., regions with higher sequence homology to other similar or equivalent antigens from other adenovirus serotypes/genotypes) may be included in a fusion protein or composition of the invention, which has the advantage, for example, of providing a broad spectrum immunotherapeutic with potential applications beyond the treatment or prevention of obesity and adipose-related conditions.

In one exemplary embodiment of the invention, the Ad-36 antigen(s) for use in a composition or method of the invention is a protein comprising Ad-36 sequences, wherein the Ad-36 sequences comprise or consist of Ad-36 fiber protein and/or one or more immunogenic domains of Ad-36 fiber protein. In one aspect, the Ad-36 fiber antigen is full-length fiber protein or near full-length fiber protein. In one aspect, the Ad-36 fiber antigen comprises at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the linear sequence of a full-length Ad-36 fiber antigen or an immunogenic domain or portion thereof. In one aspect, the Ad-36 fiber antigen is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a full-length Ad-36 fiber antigen or an immunogenic domain or portion thereof. In one embodiment, a protein useful in a composition or method of the invention comprises or consists of divergent domains or portions, i.e., relatively non-conserved domains or portions, with respect to other adenoviruses, of Ad-36 fiber protein. For example, an Ad-36 fiber protein construct according to this embodiment can be comprised of a fusion of one, two, three, four, or more different regions of Ad-36 fiber protein that are poorly conserved across human adenoviral genotypes.

Examples of such fusion proteins are described in Example 1. One Ad-36 antigen comprising fiber protein sequence described in Example 1 is a fusion protein expressed as a single polypeptide with the following sequence elements fused in frame from N- to C-terminus, represented by SEQ ID NO:42: (1) an N-terminal peptide to impart resistance to proteasomal degradation and stabilize expression (positions 1 to 6 of SEQ ID NO:42); (2) positions 71-136 of Ad-36 fiber (positions 71-136 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 7-72 of SEQ ID NO:42; (3) positions 145-169 of Ad-36 fiber (positions 145-169 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 73-97 of SEQ ID NO:42; (4) positions 290-313 of Ad-36 fiber (positions 290-313 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 98-194 of SEQ ID NO:42; (5) positions 334-363 of Ad-36 fiber (positions 334-363 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 195-224 of SEQ ID NO:42; and (6) a hexahistidine tag (positions 225-230 of SEQ ID NO:42). A nucleic acid sequence encoding the fusion protein of SEQ ID NO:42 (codon optimized for yeast expression) is also included in the present invention.

Another Ad-36 antigen comprising fiber protein sequence described in Example 1 is a fusion protein expressed as a single polypeptide with the following sequence elements fused in frame from N- to C-terminus, represented by SEQ ID NO:48: (1) an N-terminal peptide to impart resistance to proteasomal degradation and stabilize or enhance expression (SEQ ID NO:56, or positions 1 to 89 of SEQ ID NO: 48); (2) a two amino acid spacer/linker (Thr-Ser) to facilitate cloning and manipulation of the sequences (positions 90 to 91 of SEQ ID NO:48); (3) positions 71-136 of Ad-36 fiber (positions 71-136 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 92-157 of SEQ ID NO:48; (4) positions 145-169 of Ad-36 fiber (positions 145-169 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 158-182 of SEQ ID NO:48; (5) positions 290-313 of Ad-36 fiber (positions 290-313 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 183-279 of SEQ ID NO:48; (6) positions 334-363 of Ad-36 fiber (positions 334-363 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 280-309 of SEQ ID NO:48; and (7) a hexahistidine tag (positions 310-315 of SEQ ID NO:48). A nucleic acid sequence encoding the fusion protein of SEQ ID NO:48 (codon optimized for yeast expression) is also included in the present invention.

The amino acid segments used in these fusion proteins can be modified by the use of additional amino acids flanking either end of any domain; the examples provided herein are exemplary only. In addition, the N-terminal expression sequence (e.g., positions 1 to 6 of SEQ ID NO:42 or positions 1-89 of SEQ ID NO:48) and the C-terminal tag (e.g., positions 225-230 of SEQ ID NO:42 or positions 310-315 of SEQ ID NO:48) are optional, and may be selected instead from other different sequences described elsewhere herein or known in the art to improve expression, stability, and/or allow for identification and/or purification of the protein, or one or both may be omitted altogether. Furthermore, short intervening linker sequences such as that exemplified in SEQ ID NO:48 (e.g., 1, 2, 3, 4, or 5, or larger, amino acid peptides) may be introduced between portions of the fusion protein for

a variety of reasons, including the introduction of restriction enzyme sites to facilitate cloning as cleavage sites for host phagosomal proteases, to accelerate protein or antigen processing, and for future manipulation of the constructs. The amino acid sequence consisting of only the Ad-36 fiber proteins in the fusion proteins described above is represented herein by SEQ ID NO:49. SEQ ID NO:49 is a fusion protein expressed as a single polypeptide: (1) positions 71-136 of Ad-36 fiber (positions 71-136 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 1-66 of SEQ ID NO:49; (2) positions 145-169 of Ad-36 fiber (positions 145-169 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 67-91 of SEQ ID NO:49; (3) positions 290-313 of Ad-36 fiber (positions 290-313 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 92-188 of SEQ ID NO:49; and (4) positions 334-363 of Ad-36 fiber (positions 334-363 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 189-218 of SEQ ID NO:49. A nucleic acid sequence encoding the fusion protein of SEQ ID NO:49 (codon optimized for yeast expression) is also included in the present invention.

In another exemplary embodiment of the invention, the Ad-36 antigen(s) for use in a composition or method of the invention is a protein comprising Ad-36 sequences, wherein the Ad-36 sequences comprise or consist of Ad-36 hexon protein and/or one or more immunogenic domains of Ad-36 hexon protein. In one aspect, the Ad-36 hexon antigen is full-length hexon protein or near full-length hexon protein (full-length and near full-length are defined above). In one aspect, the Ad-36 hexon antigen comprises at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the linear sequence of a full-length Ad-36 hexon protein or an immunogenic domain or portion thereof. In one aspect, the Ad-36 hexon antigen is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a full-length Ad-36 hexon protein or an immunogenic domain or portion thereof. In one embodiment, a protein useful in a composition or method of the invention comprises or consists of divergent domains or portions, i.e., relatively non-conserved domains or portions, with respect to other adenoviruses, of Ad-36 hexon protein. For example, an Ad-36 hexon protein construct according to this embodiment can be comprised of a fusion of one, two, three, four, five, or more different regions of Ad-36 hexon protein that are poorly conserved across human adenoviral genotypes.

Examples of such fusion proteins comprising hexon proteins are described in Example 1. One such Ad-36 antigen comprising hexon protein sequences derived from divergent portions of Ad-36 hexon is a fusion protein expressed as a single polypeptide with the following sequence elements fused in frame from N- to C-terminus, represented by SEQ ID NO:43: (1) an N-terminal peptide to impart resistance to proteasomal degradation and stabilize expression (positions 1 to 6 of SEQ ID NO:43); (2) positions 136-218 of Ad-36 hexon (positions 136-218 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 7-89 of SEQ ID NO:43; (3) positions 235-285 of Ad-36 hexon (positions 235-285 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 90-141 of SEQ ID NO:43; (4) positions 297-308 of Ad-36 hexon (positions 297-308 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 142-153 of SEQ ID NO:43; (5) positions 410-450 of Ad-36 hexon

(positions 410-450 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 154-194 of SEQ ID NO:43; and (6) a hexahistidine tag (positions 195-200 of SEQ ID NO:43). A nucleic acid sequence encoding the fusion protein of SEQ ID NO:43 (codon optimized for yeast expression) is also included in the present invention.

Another Ad-36 antigen comprising hexon protein sequence derived from divergent portions of Ad-36 sequence is a fusion protein expressed as a single polypeptide with the following sequence elements fused in frame from N- to C-terminus, represented by SEQ ID NO:50: (1) an N-terminal peptide to impart resistance to proteasomal degradation and stabilize or enhance expression (SEQ ID NO:56, or positions 1 to 89 of SEQ ID NO:50); (2) a two amino acid spacer/linker (Thr-Ser) to facilitate cloning and manipulation of the sequences (positions 90 to 91 of SEQ ID NO:50); (3) positions 136-218 of Ad-36 hexon (positions 136-218 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 92-174 of SEQ ID NO:50; (4) positions 235-285 of Ad-36 hexon (positions 235-285 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 175-226 of SEQ ID NO:50; (5) positions 297-308 of Ad-36 hexon (positions 297-308 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 227-238 of SEQ ID NO:50; (6) positions 410-450 of Ad-36 hexon (positions 410-450 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 239-279 of SEQ ID NO:50; and (7) a hexahistidine tag (positions 280-285 of SEQ ID NO:50). A nucleic acid sequence encoding the fusion protein of SEQ ID NO: 50 (codon optimized for yeast expression) is also included in the present invention.

The amino acid segments used in these hexon-based fusion proteins described above can be modified by the use of additional amino acids flanking either end of any domain; the examples provided herein are exemplary only. In addition, the N-terminal expression sequence (e.g., positions 1 to 6 of SEQ ID NO:43 or positions 1-89 of SEQ ID NO:50) and the C-terminal tag (e.g., positions 195-200 of SEQ ID NO:43 or positions 280-285 of SEQ ID NO:50) are optional, and may be selected instead from other different sequences described elsewhere herein or known in the art to improve expression, stability, and/or allow for identification and/or purification of the protein, or one or both may be omitted altogether. Furthermore, short intervening linker sequences such as that exemplified in SEQ ID NO:48 (e.g., 1, 2, 3, 4, or 5, or larger, amino acid peptides) may be introduced between portions of the fusion protein for a variety of reasons, including the introduction of restriction enzyme sites to facilitate cloning as cleavage sites for host phagosomal proteases, to accelerate protein or antigen processing, and for future manipulation of the constructs. The amino acid sequence consisting of only the Ad-36 hexon proteins in the fusion proteins described above is represented herein by SEQ ID NO:51. SEQ ID NO:51 is a fusion protein expressed as a single polypeptide: (1) positions 136-218 of Ad-36 hexon (positions 136-218 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 1-83 of SEQ ID NO:51; (2) positions 235-285 of Ad-36 hexon (positions 235-285 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 84-135 of SEQ ID NO:51; (3) positions 297-308 of Ad-36 hexon (positions 297-308 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 136-147 of SEQ ID NO:51;

and (4) positions 410-450 of Ad-36 hexon (positions 410-450 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 148-188 of SEQ ID NO:51. Any suitable N-terminal and/or C-terminal sequence may be appended to this sequence, as described above for SEQ ID NOs:43 and 50, or one or both may be omitted. A nucleic acid sequence encoding the fusion protein of SEQ ID NO:51 (codon optimized for yeast expression) is also included in the present invention.

An Ad-36 antigen comprising full-length or near full-length hexon protein sequence described in Example 1 is a fusion protein expressed as a single polypeptide with the following sequence elements fused in frame from N- to C-terminus, represented by SEQ ID NO:44: (1) an N-terminal peptide to impart resistance to proteasomal degradation and stabilize expression (positions 1 to 6 of SEQ ID NO:44); (2) positions 2-944 of Ad-36 hexon (positions 2-944 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 7-949 of SEQ ID NO:44; and (3) a hexahistidine tag (positions 950-955 of SEQ ID NO:44). This construct contains demonstrated or putative MHC Class I epitopes (e.g., positions 119-129 of SEQ ID NO:44; positions 319-327 of SEQ ID NO:44; positions 710-718 of SEQ ID NO:44; positions 843-851 of SEQ ID NO:44; or positions 909-915 of SEQ ID NO:44), and demonstrated or putative MHC Class II epitopes (e.g., positions 15-25 of SEQ ID NO:44; positions 31-41 of SEQ ID NO:44; 321-335 of SEQ ID NO:44; positions 373-383 of SEQ ID NO:44; positions 707-718 of SEQ ID NO:44; or positions 862-872 of SEQ ID NO:44). A nucleic acid sequence encoding the fusion protein of SEQ ID NO:44 (codon optimized for yeast expression) is also included in the present invention.

Another Ad-36 antigen comprising full-length or near full-length hexon protein sequence described in Example 1 is a fusion protein expressed as a single polypeptide with the following sequence elements fused in frame from N- to C-terminus, represented by SEQ ID NO:52: (1) an N-terminal peptide to impart resistance to proteasomal degradation and stabilize or enhance expression (SEQ ID NO:56, or positions 1 to 89 of SEQ ID NO:52); (2) a two amino acid spacer/linker (Thr-Ser) to facilitate cloning and manipulation of the sequences (positions 90 to 91 of SEQ ID NO:52); (3) positions 2-944 of Ad-36 hexon (positions 2-944 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 92-1034 of SEQ ID NO:52; and (3) a hexahistidine tag (positions 1035-1040 of SEQ ID NO:52). This construct contains demonstrated or putative MHC Class I epitopes (e.g., positions 204-214 of SEQ ID NO:52; positions 404-412 of SEQ ID NO:52; positions 795-803 of SEQ ID NO:52; positions 928-936 of SEQ ID NO:52; or positions 994-1000 of SEQ ID NO:52), and demonstrated or putative MHC Class II epitopes (e.g., positions 100-110 of SEQ ID NO:52; positions 116-126 of SEQ ID NO:52; 406-420 of SEQ ID NO:52; positions 458-468 of SEQ ID NO:52; positions 792-803 of SEQ ID NO:52; or positions 947-957 of SEQ ID NO:52). A nucleic acid sequence encoding the fusion protein of SEQ ID NO:52 (codon optimized for yeast expression) is also included in the present invention.

The amino acid segments used in these hexon-based fusion proteins described above can be modified by the use of additional amino acids flanking either end of any domain; the examples provided herein are exemplary only. In addition, the N-terminal expression sequence (e.g., positions 1 to 6 of SEQ ID NO:44 or positions 1-89 of SEQ ID NO:52) and the C-terminal tag (e.g., positions 950-955 of SEQ ID NO:44 or positions 1035-1040 of SEQ ID NO:52) are optional, and

may be selected instead from other different sequences described elsewhere herein or known in the art to improve expression, stability, and/or allow for identification and/or purification of the protein, or one or both may be omitted altogether. Furthermore, short intervening linker sequences such as that exemplified in SEQ ID NO:48 (e.g., 1, 2, 3, 4, or 5, or larger, amino acid peptides) may be introduced between portions of the fusion protein for a variety of reasons, including the introduction of restriction enzyme sites to facilitate cloning as cleavage sites for host phagosomal proteases, to accelerate protein or antigen processing, and for future manipulation of the constructs. The amino acid sequence consisting of only the Ad-36 hexon protein in the fusion proteins described above is represented herein by SEQ ID NO:53. SEQ ID NO:53 is a fusion protein expressed as a single polypeptide and comprises positions 2-944 of Ad-36 hexon (positions 2-944 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 1-943 of SEQ ID NO:53. This construct contains demonstrated or putative MHC Class I epitopes (e.g., positions 113-123 of SEQ ID NO:53; positions 313-321 of SEQ ID NO:53; positions 704-712 of SEQ ID NO:53; positions 837-845 of SEQ ID NO:53; or positions 903-909 of SEQ ID NO:53), and demonstrated or putative MHC Class II epitopes (e.g., positions 9-19 of SEQ ID NO:53; positions 25-35 of SEQ ID NO:53; 315-329 of SEQ ID NO:53; positions 367-377 of SEQ ID NO:53; positions 701-712 of SEQ ID NO:53; or positions 856-866 of SEQ ID NO:53). Any suitable N-terminal and/or C-terminal sequence may be appended to this sequence, as described above for SEQ ID NOs:44 and 52, or one or both may be omitted. A nucleic acid sequence encoding the fusion protein of SEQ ID NO:53 (codon optimized for yeast expression) is also included in the present invention.

In another exemplary embodiment of the invention, the Ad-36 antigen(s) for use in a composition or method of the invention is a protein comprising Ad-36 sequences, wherein the Ad-36 sequences comprise or consist of Ad-36 hexon protein and fiber protein and/or one or more immunogenic domains of hexon protein and fiber protein. In one aspect, the Ad-36 hexon and/or the Ad-36 fiber antigen are full-length proteins or near full-length proteins (full-length and near full-length are defined above). In one aspect, the Ad-36 hexon and/or fiber antigen comprises at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the linear sequence of a full-length Ad-36 protein or immunogenic domain or portion thereof. In one aspect, the Ad-36 hexon and/or the Ad-36 fiber antigen is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a full-length Ad-36 protein or immunogenic domain or portion thereof. In one embodiment, a protein useful in a composition or method of the invention comprises or consists of divergent domains or portions, i.e., relatively non-conserved domains or portions, with respect to other adenoviruses, of Ad-36 hexon protein and Ad-36 fiber protein. For example, an Ad-36 hexon-fiber or fiber-hexon protein construct according to this embodiment can be comprised of a fusion of one, two, three, four, five, or more different regions of Ad-36 hexon protein that are poorly conserved across human adenoviral genotypes, and one, two, three, four, five or more different regions of Ad-36 fiber protein that are poorly conserved across human adenoviral genotypes.

Examples of such fusion proteins comprising both hexon and fiber proteins are described in Example 1. One such Ad-36 antigen comprising hexon and fiber protein sequences derived from divergent portions of Ad-36 hexon and fiber is a fusion protein expressed as a single polypeptide with the

following sequence elements fused in frame from N- to C-terminus, represented by SEQ ID NO:45: (1) an N-terminal peptide to impart resistance to proteasomal degradation and stabilize expression (positions 1 to 6 of SEQ ID NO:45); (2) positions 71-136 of Ad-36 fiber (positions 71-136 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 7-72 of SEQ ID NO:45; (3) positions 145-169 of Ad-36 fiber (positions 145-169 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 73-97 of SEQ ID NO:45; (4) positions 290-313 of Ad-36 fiber (positions 290-313 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 98-194 of SEQ ID NO:45; (5) positions 334-363 of Ad-36 fiber (positions 334-363 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 195-224 of SEQ ID NO:45; (6) positions 136-218 of Ad-36 hexon (positions 136-218 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 225-307 of SEQ ID NO:45; (7) positions 235-285 of Ad-36 hexon (positions 235-285 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 308-359 of SEQ ID NO:45; (8) positions 297-308 of Ad-36 hexon (positions 297-308 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 360-371 of SEQ ID NO:45; (9) positions 410-450 of Ad-36 hexon (positions 410-450 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 372-412 of SEQ ID NO:45; and (10) a hexahistidine tag (positions 413-418 of SEQ ID NO:45).

Another Ad-36 antigen comprising hexon and fiber protein sequences derived from divergent portions of Ad-36 hexon and fiber is a fusion protein expressed as a single polypeptide with the following sequence elements fused in frame from N- to C-terminus, represented by SEQ ID NO:46: (1) an N-terminal peptide to impart resistance to proteasomal degradation and stabilize expression (positions 1 to 6 of SEQ ID NO:46); (2) positions 136-218 of Ad-36 hexon (positions 136-218 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 7-89 of SEQ ID NO:46; (3) positions 235-285 of Ad-36 hexon (positions 235-285 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 90-141 of SEQ ID NO:46; (4) positions 297-308 of Ad-36 hexon (positions 297-308 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 142-153 of SEQ ID NO:46; (5) positions 410-450 of Ad-36 hexon (positions 410-450 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 154-194 of SEQ ID NO:46; (6) positions 71-136 of Ad-36 fiber (positions 71-136 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 195-260 of SEQ ID NO:46; (7) positions 145-169 of Ad-36 fiber (positions 145-169 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 261-285 of SEQ ID NO:46; (8) positions 290-313 of Ad-36 fiber (positions 290-313 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 286-382 of SEQ ID NO:46; (9) positions 334-363 of Ad-36 fiber (positions 334-363 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 383-412 of SEQ ID NO:46; and (10) a hexahistidine tag (positions 413-418 of SEQ ID NO:46). A nucleic acid

sequence encoding the fusion protein of SEQ ID NO:45 or SEQ ID NO:46 (codon optimized for yeast expression) is also included in the present invention.

The amino acid segments used in any of the fusion proteins described above can be modified by the use of additional amino acids flanking either end of any domain; the examples provided herein are exemplary only. The N-terminal expression sequence (positions 1 to 6 of SEQ ID NO:45 or 46) and the C-terminal tag (positions 413-418 of SEQ ID NO:45 or 46) are optional, and may be selected instead from other different sequences described elsewhere herein or known in the art to improve expression, stability, and/or allow for identification and/or purification of the protein, or one or both may be omitted altogether. Furthermore, short intervening linker sequences such as that exemplified in SEQ ID NO:48 (e.g., 1, 2, 3, 4, or 5, or larger, amino acid peptides) may be introduced between portions of the fusion protein for a variety of reasons, including the introduction of restriction enzyme sites to facilitate cloning as cleavage sites for host phagosomal proteases, to accelerate protein or antigen processing, and for future manipulation of the constructs. For example, a fusion protein omitting both the N- and C-terminal sequences of SEQ ID NO:45 is represented by positions 7-412 of SEQ ID NO:45 and a fusion protein omitting both the N- and C-terminal sequences of SEQ ID NO:46 is represented by positions 7-412 of SEQ ID NO:46.

In yet another exemplary embodiment of the invention, the Ad-36 antigen(s) for use in a composition or method of the invention is a protein comprising Ad-36 sequences, wherein the Ad-36 sequences comprise or consist of Ad-36 CR1 α protein and/or Ad-36 CR1 γ and/or one or more immunogenic domains of CR1 α and/or CR1 γ . In one aspect, the Ad-36 CR1 α and/or the Ad-36 CR1 γ antigen are full-length proteins or near full-length proteins (full-length and near full-length are defined above). In one aspect, the Ad-36 CR1 α and/or the Ad-36 CR1 γ antigen comprises at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the linear sequence of a full-length Ad-36 protein or immunogenic domain or portion thereof. In one aspect, the Ad-36 CR1 α and/or the Ad-36 CR1 γ antigen is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a full-length Ad-36 protein or immunogenic domain or portion thereof. In one embodiment, a protein useful in a composition or method of the invention comprises or consists of divergent domains or portions, i.e., relatively non-conserved domains or portions, with respect to other adenoviruses, of Ad-36 CR1 α and/or CR1 γ . For example, an Ad-36 CR1 α and/or CR1 γ protein construct according to this embodiment can be comprised of a fusion of one, two, three, four, five, or more different regions of Ad-36 CR1 α and/or CR1 γ protein that are poorly conserved across human adenoviral genotypes. In one embodiment, a notably hydrophobic N-terminal region is omitted from CR1 α in a protein of the invention (e.g., about positions 1-17 of the mature protein) to minimize the risk of aggregation and/or insolubility when that protein is expressed in yeast. In one embodiment, a C-terminal segment of mature CR1 α is omitted from proteins used in the invention because of notable hydrophobicity (positions 158-177) plus high sequence conservation with other adenovirus serotypes/genotypes (positions 158 through C-terminus). In another embodiment, the N-terminal positions 1-18 of CR1 γ are omitted from proteins used in the invention as they contain both highly conserved amino acid positions with other adenovirus serotypes/genotypes, and they also contain a very hydrophobic element.

Examples of such fusion proteins comprising both CR1 α and CR1 γ proteins are described in Example 1. One such

Ad-36 antigen comprising CR1 α and CR1 γ protein sequences derived from divergent and/or selected portions of Ad-36 CR1 α and CR1 γ is a fusion protein expressed as a single polypeptide with the following sequence elements fused in frame from N- to C-terminus, represented by SEQ ID NO:47: (1) an N-terminal peptide to impart resistance to proteasomal degradation and stabilize expression (positions 1 to 6 of SEQ ID NO:47); (2) positions 18-60 of CR1 α (positions 18-60 of SEQ ID NO:26 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 7-49 of SEQ ID NO:47; (3) positions 123-157 of Ad-36 CR1 α (positions 123-157 of SEQ ID NO:26 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 50-84 of SEQ ID NO:47; (4) positions 19-60 of Ad-36 CR1 γ (positions 19-60 of SEQ ID NO:29 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 85-126 of SEQ ID NO:47; (5) positions 83-116 of Ad-36 CR1 γ (positions 83-116 of SEQ ID NO:29 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 127-160 of SEQ ID NO:47; and (6) a hexahistidine tag (positions 161-166 of SEQ ID NO:47). The amino acid segments used in any of the fusion proteins described above can be modified by the use of additional amino acids flanking either end of any domain; the examples provided herein are exemplary only. A nucleic acid sequence encoding the fusion protein of SEQ ID NO:47 (codon optimized for yeast expression) is also included in the present invention.

Another Ad-36 antigen comprising CR1 α and CR1 γ protein sequences described in Example 1 is a fusion protein expressed as a single polypeptide with the following sequence elements fused in frame from N- to C-terminus, represented by SEQ ID NO:54: (1) an N-terminal peptide to impart resistance to proteasomal degradation and stabilize or enhance expression (SEQ ID NO:56, or positions 1 to 89 of SEQ ID NO:54); (2) a two amino acid spacer/linker (Thr-Ser) to facilitate cloning and manipulation of the sequences (positions 90 to 91 of SEQ ID NO:54); (3) positions 18-60 of CR1 α (positions 18-60 of SEQ ID NO:26 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 92-134 of SEQ ID NO:54; (4) positions 123-157 of Ad-36 CR1 α (positions 123-157 of SEQ ID NO:26 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 135-169 of SEQ ID NO:54; (5) positions 19-60 of Ad-36 CR1 γ (positions 19-60 of SEQ ID NO:29 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 170-211 of SEQ ID NO:54; (6) positions 83-116 of Ad-36 CR1 γ (positions 83-116 of SEQ ID NO:29 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 212-245 of SEQ ID NO:54; and (7) a hexahistidine tag (positions 246-251 of SEQ ID NO:54). A nucleic acid sequence encoding the fusion protein of SEQ ID NO:54 (codon optimized for yeast expression) is also included in the present invention.

The amino acid segments used in these CR1 α and CR1 γ -based fusion proteins described above can be modified by the use of additional amino acids flanking either end of any domain; the examples provided herein are exemplary only. In addition, the N-terminal expression sequence (e.g., positions 1 to 6 of SEQ ID NO:47 or positions 1-89 of SEQ ID NO:54) and the C-terminal tag (e.g., positions 161-166 of SEQ ID NO:47 or positions 246-251 of SEQ ID NO:54) are optional, and may be selected instead from other different sequences described elsewhere herein or known in the art to improve expression, stability, and/or allow for identification and/or purification of the protein, or one or both may be omitted

altogether. Furthermore, short intervening linker sequences such as that exemplified in SEQ ID NO:48 (e.g., 1, 2, 3, 4, or 5, or larger, amino acid peptides) may be introduced between portions of the fusion protein for a variety of reasons, including the introduction of restriction enzyme sites to facilitate cloning as cleavage sites for host phagosomal proteases, to accelerate protein or antigen processing, and for future manipulation of the constructs. The amino acid sequence consisting of only the Ad-36 CR1 α and CR1 γ proteins in the fusion proteins described above is represented herein by SEQ ID NO:55. SEQ ID NO:55 is a fusion protein expressed as a single polypeptide: (1) positions 18-60 of CR1 α (positions 18-60 of SEQ ID NO:26 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 1-43 of SEQ ID NO:55; (2) positions 123-157 of Ad-36 CR1 α (positions 123-157 of SEQ ID NO:26 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 44-78 of SEQ ID NO:55; (3) positions 19-60 of Ad-36 CR1 γ (positions 19-60 of SEQ ID NO:29 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 79-120 of SEQ ID NO:55; and (4) positions 83-116 of Ad-36 CR1 γ (positions 83-116 of SEQ ID NO:29 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 121-154 of SEQ ID NO:55. Any suitable N-terminal and/or C-terminal sequence may be appended to this sequence, as described above for SEQ ID NOs:47 and 54, or one or both may be omitted. A nucleic acid sequence encoding the fusion protein of SEQ ID NO:55 (codon optimized for yeast expression) is also included in the present invention.

The invention also includes homologues of any of the above-described fusion proteins, as well as the use of homologues, variants, or mutants of the individual Ad-36 proteins or portions thereof that are part of such fusion proteins. In one aspect, the invention includes the use of fusion proteins having amino acid sequences that are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the amino acid sequence of the fusion proteins described herein over the full length of the fusion protein, or with respect to a defined protein or domain thereof (immunological domain or functional domain (domain with at least one biological activity)) that forms part of the fusion protein.

Recombinant nucleic acid molecules useful in a yeast-based composition of the invention do not include the full length genome of Ad-36, but rather include less than the full-length Ad-36 genome. Typically, recombinant nucleic acid molecules useful in a yeast-based composition of the invention include one or more full-length coding sequences and/or one or more coding sequences of domains (immunogenic or functional) for Ad-36 proteins. Proteins included in a single yeast-based composition of the invention do not include all of the proteins encoded by Ad-36. Preferably, a yeast-based composition comprises one, two, three, four, five, six, seven, eight, nine, ten or more proteins encoded by Ad-36, and/or one or more immunogenic domains of any one or more Ad-36 proteins.

Recombinant nucleic acid molecules and the proteins encoded thereby, including fusion proteins, as one embodiment of the invention, may be used in yeast-based immunotherapy compositions, or for any other suitable purpose for an Ad-36 antigen(s), including in an in vitro assay, for the production of antibodies, or in another immunotherapy composition, including another vaccine, that is not based on the yeast-based immunotherapy described herein. Expression of the proteins/antigens by yeast is one preferred embodiment,

although other expression systems may be used to produce the proteins/antigens for applications other than a yeast-based immunotherapy composition.

Yeast-Based Immunotherapy Compositions. In various embodiments of the invention, the invention includes the use of at least one “yeast-based immunotherapeutic composition” (which phrase may be used interchangeably with “yeast-based immunotherapy product”, “yeast-based immunotherapy composition”, “yeast-based composition”, “yeast-based immunotherapeutic”, “yeast-based vaccine”, or derivatives of these phrases). An “immunotherapeutic composition” is a composition that elicits an immune response sufficient to achieve at least one therapeutic benefit in a subject. As used herein, yeast-based immunotherapeutic composition refers to a composition that includes a yeast vehicle component and that elicits an immune response sufficient to achieve at least one therapeutic benefit in a subject. More particularly, a yeast-based immunotherapeutic composition is a composition that includes a yeast vehicle component and can elicit or induce an immune response, such as a cellular immune response, including without limitation a T cell-mediated cellular immune response. In one aspect, a yeast-based immunotherapeutic composition useful in the invention is capable of inducing a CD8⁺ and/or a CD4⁺ T cell-mediated immune response and in one aspect, a CD8⁺ and a CD4⁺ T cell-mediated immune response. A CD4⁺ immune response can include TH1 immune responses, TH17 immune responses, or both, as yeast-based immunotherapeutics are capable of generating both types of response. A CD8⁺ immune response can include a cytotoxic T lymphocyte (CTL) response, as yeast-based immunotherapeutics are capable of generating such responses. In one aspect, a yeast-based immunotherapeutic composition modulates the number and/or functionality of regulatory T cells (Tregs) in a subject. Yeast-based immunotherapy can also be modified to promote one type of response over another, e.g., by the addition of cytokines, antibodies, and/or modulating the manufacturing process for the yeast. Optionally, a yeast-based immunotherapeutic composition is capable of eliciting a humoral immune response. A yeast-based immunotherapeutic composition useful in the present invention can, for example, elicit an immune response in an individual such that the individual is protected from Ad-36 infection and/or is treated for Ad-36 infection or for symptoms resulting from Ad-36 infection.

Yeast-based immunotherapy compositions of the invention may be either “prophylactic” or “therapeutic”. When provided prophylactically, the compositions of the present invention are provided in advance of any symptom of Ad-36 infection. Such a composition could be administered at birth, in early childhood, or to adults, and can include obese, overweight, non-obese, and non-overweight subjects. The prophylactic administration of the immunotherapy compositions serves to prevent subsequent Ad-36 infection, to resolve an infection more quickly or more completely if Ad-36 infection subsequently ensues, and/or to prevent or ameliorate the symptoms of Ad-36 infection if infection subsequently ensues. When provided therapeutically, the immunotherapy compositions are provided at or after the onset of Ad-36 infection, with the goal of preventing or ameliorating at least one symptom of the infection (e.g., preventing obesity in non-obese, Ad-36-infected subjects, or reducing weight in obese, Ad-36-infected subjects) and preferably, with a goal of eliminating the infection, providing a long lasting remission of infection, and/or providing long term immunity against subsequent infections or reactivations of the virus.

Typically, a yeast-based immunotherapy composition includes a yeast vehicle and at least one antigen (e.g., an Ad-36 protein) or immunogenic domain thereof expressed by, attached to, or mixed with the yeast vehicle, wherein the antigen is heterologous to the yeast, and wherein the antigen comprises one or more Ad-36 proteins or immunogenic domains thereof. In some embodiments, the antigen or immunogenic domain thereof is provided as a fusion protein. Several Ad-36 fusion proteins suitable for use in the compositions and methods of the invention have been described above. In one aspect of the invention, fusion protein can include two or more antigens. In one aspect, the fusion protein can include two or more immunogenic domains of one or more antigens, or two or more epitopes of one or more antigens.

A TARMOGEN® is one non-limiting example of a yeast-based immunotherapy composition that is useful in the present invention. A TARMOGEN® (TARgeted MOlecular immunoGEN, GlobeImmune, Inc., Louisville, Colo.) generally refers to a yeast vehicle expressing one or more heterologous antigens extracellularly (on its surface), intracellularly (internally or cytosolically) or both extracellularly and intracellularly. TARMOGEN®s have been generally described in the art. See, e.g., U.S. Pat. No. 5,830,463.

Yeast-based immunotherapy compositions, and methods of making and generally using the same, are described in detail, for example, in U.S. Pat. No. 5,830,463, U.S. Pat. No. 7,083,787, U.S. Pat. No. 7,736,642, Stubbs et al., *Nat. Med.* 7:625-629 (2001), Lu et al., *Cancer Research* 64:5084-5088 (2004), and in Bernstein et al., *Vaccine* 2008 Jan. 24; 26(4): 509-21, each of which is incorporated herein by reference in its entirety. These yeast-based immunotherapeutic products have been shown to elicit immune responses, including cellular and humoral immune responses. Yeast-based immunotherapeutic products are capable of killing target cells expressing a variety of antigens in vivo, in a variety of animal species, and to do so via antigen-specific, CD4⁺ and CD8⁺ T cell-mediated immune responses. Additional studies have shown that yeast are avidly phagocytosed by and directly activate dendritic cells which then present yeast-associated proteins to CD4⁺ and CD8⁺ T cells in a highly efficient manner. See, e.g., Stubbs et al. *Nature Med.* 5:625-629 (2001) and U.S. Pat. No. 7,083,787.

In any of the yeast-based immunotherapy compositions used in the present invention, the following aspects related to the yeast vehicle are included in the invention. According to the present invention, a yeast vehicle is any yeast cell (e.g., a whole or intact cell) or a derivative thereof (see below) that can be used in conjunction with one or more antigens, immunogenic domains thereof or epitopes thereof in a therapeutic composition of the invention, or in one aspect, the yeast vehicle can be used alone or as an adjuvant. The yeast vehicle can therefore include, but is not limited to, a live intact (whole) yeast microorganism (i.e., a yeast cell having all its components including a cell wall), a killed (dead) or inactivated intact yeast microorganism, or derivatives of intact yeast including: a yeast spheroplast (i.e., a yeast cell lacking a cell wall), a yeast cytoplasm (i.e., a yeast cell lacking a cell wall and nucleus), a yeast ghost (i.e., a yeast cell lacking a cell wall, nucleus and cytoplasm), a subcellular yeast membrane extract or fraction thereof (also referred to as a yeast membrane particle and previously as a subcellular yeast particle), any other yeast particle, or a yeast cell wall preparation.

Yeast spheroplasts are typically produced by enzymatic digestion of the yeast cell wall. Such a method is described, for example, in Franzusoff et al., 1991, *Meth. Enzymol.* 194, 662-674, incorporated herein by reference in its entirety.

Yeast cytoplasts are typically produced by enucleation of yeast cells. Such a method is described, for example, in Coon, 1978, *Natl. Cancer Inst. Monogr.* 48, 45-55 incorporated herein by reference in its entirety.

Yeast ghosts are typically produced by resealing a permeabilized or lysed cell and can, but need not, contain at least some of the organelles of that cell. Such a method is described, for example, in Franzusoff et al., 1983, *J. Biol. Chem.* 258, 3608-3614 and Bussey et al., 1979, *Biochim. Biophys. Acta* 553, 185-196, each of which is incorporated herein by reference in its entirety.

A yeast membrane particle (subcellular yeast membrane extract or fraction thereof) refers to a yeast membrane that lacks a natural nucleus or cytoplasm. The particle can be of any size, including sizes ranging from the size of a natural yeast membrane to microparticles produced by sonication or other membrane disruption methods known to those skilled in the art, followed by resealing. A method for producing subcellular yeast membrane extracts is described, for example, in Franzusoff et al., 1991, *Meth. Enzymol.* 194, 662-674. One may also use fractions of yeast membrane particles that contain yeast membrane portions and, when the antigen or other protein was expressed recombinantly by the yeast prior to preparation of the yeast membrane particles, the antigen or other protein of interest. Antigens or other proteins of interest can be carried inside the membrane, on either surface of the membrane, or combinations thereof (i.e., the protein can be both inside and outside the membrane and/or spanning the membrane of the yeast membrane particle). In one embodiment, a yeast membrane particle is a recombinant yeast membrane particle that can be an intact, disrupted, or disrupted and resealed yeast membrane that includes at least one desired antigen or other protein of interest on the surface of the membrane or at least partially embedded within the membrane.

An example of a yeast cell wall preparation is a preparation of isolated yeast cell walls carrying an antigen on its surface or at least partially embedded within the cell wall such that the yeast cell wall preparation, when administered to an animal, stimulates a desired immune response against a disease target.

Any yeast strain can be used to produce a yeast vehicle of the present invention. Yeast are unicellular microorganisms that belong to one of three classes: Ascomycetes, Basidiomycetes and Fungi Imperfecti. One consideration for the selection of a type of yeast for use as an immune modulator is the pathogenicity of the yeast. In one embodiment, the yeast is a non-pathogenic strain such as *Saccharomyces cerevisiae*. The selection of a non-pathogenic yeast strain minimizes any adverse effects to the individual to whom the yeast vehicle is administered. However, pathogenic yeast may be used if the pathogenicity of the yeast can be negated by any means known to one of skill in the art (e.g., mutant strains). In accordance with one aspect of the present invention, non-pathogenic yeast strains are used.

Genera of yeast strains that may be used in the invention include but are not limited to *Saccharomyces*, *Candida* (which can be pathogenic), *Cryptococcus*, *Hansenula*, *Kluyveromyces*, *Pichia*, *Rhodotorula*, *Schizosaccharomyces* and *Yarrowia*. In one aspect, yeast genera are selected from *Saccharomyces*, *Candida*, *Hansenula*, *Pichia* or *Schizosaccharomyces*, and in one aspect, *Saccharomyces* is used. Species of yeast strains that may be used in the invention include but are not limited to *Saccharomyces cerevisiae*, *Saccharomyces carlsbergensis*, *Candida albicans*, *Candida kefyr*, *Candida tropicalis*, *Cryptococcus laurentii*, *Cryptococcus neoformans*, *Hansenula anomala*, *Hansenula polymorpha*,

Kluyveromyces fragilis, *Kluyveromyces lactis*, *Kluyveromyces marxianus* var. *lactis*, *Pichia pastoris*, *Rhodotorula rubra*, *Schizosaccharomyces pombe*, and *Yarrowia lipolytica*. It is to be appreciated that a number of these species include a variety of subspecies, types, subtypes, etc. that are intended to be included within the aforementioned species. In one aspect, yeast species used in the invention include *S. cerevisiae*, *C. albicans*, *H. polymorpha*, *P. pastoris* and *S. pombe*. *S. cerevisiae* is useful as it is relatively easy to manipulate and being "Generally Recognized As Safe" or "GRAS" for use as food additives (GRAS, FDA proposed Rule 62FR18938, Apr. 17, 1997). One embodiment of the present invention is a yeast strain that is capable of replicating plasmids to a particularly high copy number, such as a *S. cerevisiae* cir^o strain. The *S. cerevisiae* strain is one such strain that is capable of supporting expression vectors that allow one or more target antigen(s) and/or antigen fusion protein(s) and/or other proteins to be expressed at high levels. In addition, any mutant yeast strains can be used in the present invention, including those that exhibit reduced post-translational modifications of expressed target antigens or other proteins, such as mutations in the enzymes that extend N-linked glycosylation.

In one embodiment, a yeast vehicle of the present invention is capable of fusing with the cell type to which the yeast vehicle and antigen/agent is being delivered, such as a dendritic cell or macrophage, thereby effecting particularly efficient delivery of the yeast vehicle, and in many embodiments, the antigen(s) or other agent, to the cell type. As used herein, fusion of a yeast vehicle with a targeted cell type refers to the ability of the yeast cell membrane, or particle thereof, to fuse with the membrane of the targeted cell type (e.g., dendritic cell or macrophage), leading to syncytia formation. As used herein, a syncytium is a multinucleate mass of protoplasm produced by the merging of cells. A number of viral surface proteins (including those of immunodeficiency viruses such as HIV, influenza virus, poliovirus and adenovirus) and other fusogens (such as those involved in fusions between eggs and sperm) have been shown to be able to effect fusion between two membranes (i.e., between viral and mammalian cell membranes or between mammalian cell membranes). It is noted, however, that incorporation of a targeting moiety into the yeast vehicle, while it may be desirable under some circumstances, is not necessary. In the case of yeast vehicles that express antigens extracellularly, this can be a further advantage of the yeast vehicles of the present invention. In general, yeast vehicles useful in the present invention are readily taken up by dendritic cells (as well as other cells, such as macrophages).

In most embodiments of the invention, the yeast-based immunotherapy composition includes at least one antigen, immunogenic domain thereof, or epitope thereof. The antigens contemplated for use in this invention include any Ad-36 antigen or immunogenic domain thereof, including mutants, variants and agonists of Ad-36 proteins or domains thereof, against which it is desired to elicit an immune response for the purpose of prophylactically or therapeutically immunizing a host against Ad-36 infection.

As discussed above, the compositions of the invention include at least one Ad-36 antigen and/or at least one immunogenic domain of at least one Ad-36 antigen for immunizing a subject. In some embodiments, the antigen is a fusion protein, several examples of which have been described above.

Optionally, proteins, including fusion proteins, which are used as a component of the yeast-based immunotherapeutic composition of the invention are produced using constructs that are particularly useful for improving the expression of heterologous antigens in yeast. Typically, the desired anti-

genic protein(s) or peptide(s) are fused at their amino-terminal end to: (a) a specific synthetic peptide that stabilizes the expression of the fusion protein in the yeast vehicle or prevents posttranslational modification of the expressed fusion protein (such peptides are described in detail, for example, in U.S. Patent Publication No. 2004-0156858 A1, published Aug. 12, 2004, incorporated herein by reference in its entirety); (b) at least a portion of an endogenous yeast protein, wherein either fusion partner provides improved stability of expression of the protein in the yeast and/or a prevents post-translational modification of the proteins by the yeast cells (such proteins are also described in detail, for example, in U.S. Patent Publication No. 2004-0156858 A1, supra); and/or (c) at least a portion of a yeast protein that causes the fusion protein to be expressed on the surface of the yeast (e.g., an Aga protein, described in more detail herein). In addition, the present invention optionally includes the use of peptides that are fused to the C-terminus of the antigen-encoding construct, particularly for use in the selection and identification of the protein. Such peptides include, but are not limited to, any synthetic or natural peptide, such as a peptide tag (e.g., 6xHis) or any other short epitope tag. Peptides attached to the C-terminus of an antigen according to the invention can be used with or without the addition of the N-terminal peptides discussed above.

In one embodiment, a synthetic peptide useful in a fusion protein is linked to the N-terminus of the antigen, the peptide consisting of at least two amino acid positions that are heterologous to the antigen, wherein the peptide stabilizes the expression of the fusion protein in the yeast vehicle or prevents posttranslational modification of the expressed fusion protein. The synthetic peptide and N-terminal portion of the antigen together form a fusion protein that has the following requirements: (1) the amino acid residue at position one of the fusion protein is a methionine (i.e., the first amino acid in the synthetic peptide is a methionine); (2) the amino acid residue at position two of the fusion protein is not a glycine or a proline (i.e., the second amino acid in the synthetic peptide is not a glycine or a proline); (3) none of the amino acid positions at positions 2-6 of the fusion protein is a methionine (i.e., the amino acids at positions 2-6, whether part of the synthetic peptide or the protein, if the synthetic peptide is shorter than 6 amino acids, do not include a methionine); and (4) none of the amino acids at positions 2-6 of the fusion protein is a lysine or an arginine (i.e., the amino acids at positions 2-6, whether part of the synthetic peptide or the protein, if the synthetic peptide is shorter than 5 amino acids, do not include a lysine or an arginine). The synthetic peptide can be as short as two amino acids, but in one aspect, is 2-6 amino acids (including 3, 4, 5 amino acids), and can be longer than 6 amino acids, in whole integers, up to about 200 amino acids, 300 amino acids, 400 amino acids, 500 amino acids, or more.

In one embodiment, a fusion protein comprises an amino acid sequence of M-X2-X3-X4-X5-X6, wherein M is methionine; wherein X2 is any amino acid except glycine, proline, lysine or arginine; wherein X3 is any amino acid except methionine, lysine or arginine; wherein X4 is any amino acid except methionine, lysine or arginine; wherein X5 is any amino acid except methionine, lysine or arginine; and wherein X6 is any amino acid except methionine, lysine or arginine. In one embodiment, the X6 residue is a proline. An exemplary synthetic sequence that enhances the stability of expression of an antigen in a yeast cell and/or prevents post-translational modification of the protein in the yeast includes the sequence M-A-D-E-A-P (e.g., SEQ ID NO:58). Another exemplary synthetic sequence with the same properties is

M-V. In addition to the enhanced stability of the expression product, this fusion partner does not appear to negatively impact the immune response against the immunizing antigen in the construct. In addition, the synthetic fusion peptides can be designed to provide an epitope that can be recognized by a selection agent, such as an antibody.

In one aspect of the invention, the yeast vehicle is manipulated such that the antigen is expressed or provided by delivery or translocation of an expressed protein product, partially or wholly, on the surface of the yeast vehicle (extracellular expression). One method for accomplishing this aspect of the invention is to use a spacer arm for positioning one or more protein(s) on the surface of the yeast vehicle. For example, one can use a spacer arm to create a fusion protein of the antigen(s) or other protein of interest with a protein that targets the antigen(s) or other protein of interest to the yeast cell wall. For example, one such protein that can be used to target other proteins is a yeast protein (e.g., cell wall protein 2 (cwp2), Aga2, Pir4 or Flo1 protein) that enables the antigen(s) or other protein to be targeted to the yeast cell wall such that the antigen or other protein is located on the surface of the yeast. Proteins other than yeast proteins may be used for the spacer arm; however, for any spacer arm protein, it is most desirable to have the immunogenic response be directed against the target antigen rather than the spacer arm protein. As such, if other proteins are used for the spacer arm, then the spacer arm protein that is used should not generate such a large immune response to the spacer arm protein itself such that the immune response to the target antigen(s) is overwhelmed. One of skill in the art should aim for a small immune response to the spacer arm protein relative to the immune response for the target antigen(s). Spacer arms can be constructed to have cleavage sites (e.g., protease cleavage sites) that allow the antigen to be readily removed or processed away from the yeast, if desired. Any known method of determining the magnitude of immune responses can be used (e.g., antibody production, lytic assays, etc.) and are readily known to one of skill in the art.

Another method for positioning the target antigen(s) or other proteins to be exposed on the yeast surface is to use signal sequences such as glycosylphosphatidyl inositol (GPI) to anchor the target to the yeast cell wall. Alternatively, positioning can be accomplished by appending signal sequences that target the antigen(s) or other proteins of interest into the secretory pathway via translocation into the endoplasmic reticulum (ER) such that the antigen binds to a protein which is bound to the cell wall (e.g., cwp).

In one aspect, the spacer arm protein is a yeast protein. The yeast protein can consist of between about two and about 800 amino acids of a yeast protein. In one embodiment, the yeast protein is about 10 to 700 amino acids. In another embodiment, the yeast protein is about 40 to 600 amino acids. Other embodiments of the invention include the yeast protein being at least 250 amino acids, at least 300 amino acids, at least 350 amino acids, at least 400 amino acids, at least 450 amino acids, at least 500 amino acids, at least 550 amino acids, at least 600 amino acids, or at least 650 amino acids. In one embodiment, the yeast protein is at least 450 amino acids in length. Another consideration for optimizing antigen surface expression, if that is desired, is whether the antigen and spacer arm combination should be expressed as a monomer or as dimer or as a trimer, or even more units connected together. This use of monomers, dimers, trimers, etc. allows for appropriate spacing or folding of the antigen such that some part, if not all, of the antigen is displayed on the surface of the yeast vehicle in a manner that makes it more immunogenic.

Use of yeast proteins can stabilize the expression of fusion proteins in the yeast vehicle, prevents posttranslational modification of the expressed fusion protein, and/or targets the fusion protein to a particular compartment in the yeast (e.g., to be expressed on the yeast cell surface). For delivery into the yeast secretory pathway, exemplary yeast proteins to use include, but are not limited to: Aga (including, but not limited to, Aga1 and/or Aga2); SUC2 (yeast invertase); alpha factor signal leader sequence; CPY; Cwp2p for its localization and retention in the cell wall; BUD genes for localization at the yeast cell bud during the initial phase of daughter cell formation; Flo1p; Pir2p; and Pir4p.

Other sequences can be used to target, retain and/or stabilize the protein to other parts of the yeast vehicle, for example, in the cytosol or the mitochondria or the endoplasmic reticulum or the nucleus. Examples of suitable yeast protein that can be used for any of the embodiments above include, but are not limited to, TK, AF, SECT; phosphoenolpyruvate carboxykinase PCK1, phosphoglycerokinase PGK and triose phosphate isomerase TPI gene products for their repressible expression in glucose and cytosolic localization; the heat shock proteins SSA1, SSA3, SSA4, SSC1, whose expression is induced and whose proteins are more thermostable upon exposure of cells to heat treatment; the mitochondrial protein CYC1 for import into mitochondria; ACT1.

In one embodiment, the Ad-36 antigen is linked at the N-terminus to a yeast protein, such as an alpha factor prepro sequence (also referred to as the alpha factor signal leader sequence, the amino acid sequence of which is exemplified herein by SEQ ID NO:56 or SEQ ID NO:57. Other sequences for yeast alpha factor prepro sequence are known in the art and are encompassed for use in the present invention. Without being bound by theory, the inventors believe that one advantage of utilizing alpha factor prepro sequence in a yeast-based fusion protein is the minimization of proteolysis of the protein, since the protein is sequestered away from cytosolic proteasomes.

Methods of producing yeast vehicles and expressing, combining and/or associating yeast vehicles with antigens and/or other proteins and/or agents of interest to produce yeast-based immunotherapy compositions are contemplated by the invention.

According to the present invention, the term "yeast vehicle-antigen complex" or "yeast-antigen complex" is used generically to describe any association of a yeast vehicle with an antigen, and can be used interchangeably with "yeast-based immunotherapy composition" when such composition is used to elicit an immune response as described above. Such association includes expression of the antigen by the yeast (a recombinant yeast), introduction of an antigen into a yeast, physical attachment of the antigen to the yeast, and mixing of the yeast and antigen together, such as in a buffer or other solution or formulation. These types of complexes are described in detail below.

In one embodiment, a yeast cell used to prepare the yeast vehicle is transfected with a heterologous nucleic acid molecule encoding a protein (e.g., the antigen) such that the protein is expressed by the yeast cell. Such a yeast is also referred to herein as a recombinant yeast or a recombinant yeast vehicle. The yeast cell can then be loaded into the dendritic cell as an intact cell, or the yeast cell can be killed, or it can be derivatized such as by formation of yeast spheroplasts, cytoplasts, ghosts, or subcellular particles, any of which is followed by loading of the derivative into the dendritic cell. Yeast spheroplasts can also be directly transfected with a recombinant nucleic acid molecule (e.g., the spheroplast

is produced from a whole yeast, and then transfected) in order to produce a recombinant spheroplast that expresses an antigen or other protein.

In one aspect, a yeast cell or yeast spheroplast used to prepare the yeast vehicle is transfected with a recombinant nucleic acid molecule encoding the antigen(s) or other protein such that the antigen or other protein is recombinantly expressed by the yeast cell or yeast spheroplast. In this aspect, the yeast cell or yeast spheroplast that recombinantly expresses the antigen(s) or other protein is used to produce a yeast vehicle comprising a yeast cytoplast, a yeast ghost, or a yeast membrane particle or yeast cell wall particle, or fraction thereof.

In general, the yeast vehicle and antigen(s) and/or other agents can be associated by any technique described herein. In one aspect, the yeast vehicle was loaded intracellularly with the antigen(s) and/or agent(s). In another aspect, the antigen(s) and/or agent(s) was covalently or non-covalently attached to the yeast vehicle. In yet another aspect, the yeast vehicle and the antigen(s) and/or agent(s) were associated by mixing. In another aspect, and in one embodiment, the antigen(s) and/or agent(s) is expressed recombinantly by the yeast vehicle or by the yeast cell or yeast spheroplast from which the yeast vehicle was derived.

A number of antigens and/or other proteins to be produced by a yeast vehicle of the present invention is any number of antigens and/or other proteins that can be reasonably produced by a yeast vehicle, and typically ranges from at least one to at least about 6 or more, including from about 2 to about 6 heterologous antigens and or other proteins.

Expression of an antigen or other protein in a yeast vehicle of the present invention is accomplished using techniques known to those skilled in the art. Briefly, a nucleic acid molecule encoding at least one desired antigen or other protein is inserted into an expression vector in such a manner that the nucleic acid molecule is operatively linked to a transcription control sequence in order to be capable of effecting either constitutive or regulated expression of the nucleic acid molecule when transformed into a host yeast cell. Nucleic acid molecules encoding one or more antigens and/or other proteins can be on one or more expression vectors operatively linked to one or more expression control sequences. Particularly important expression control sequences are those which control transcription initiation, such as promoter and upstream activation sequences. Any suitable yeast promoter can be used in the present invention and a variety of such promoters are known to those skilled in the art. Promoters for expression in *Saccharomyces cerevisiae* include, but are not limited to, promoters of genes encoding the following yeast proteins: alcohol dehydrogenase I (ADH1) or II (ADH2), CUP1, phosphoglycerate kinase (PGK), triose phosphate isomerase (TPI), translational elongation factor EF-1 alpha (TEF2), glyceraldehyde-3-phosphate dehydrogenase (GAPDH; also referred to as TDH3, for triose phosphate dehydrogenase), galactokinase (GAL1), galactose-1-phosphate uridyl-transferase (GAL7), UDP-galactose epimerase (GAL10), cytochrome c1 (CYC1), Sec7 protein (SECT) and acid phosphatase (PHO5), including hybrid promoters such as ADH2/GAPDH and CYC1/GAL10 promoters, and including the ADH2/GAPDH promoter, which is induced when glucose concentrations in the cell are low (e.g., about 0.1 to about 0.2 percent), as well as the CUP1 promoter and the TEF2 promoter. Likewise, a number of upstream activation sequences (UASs), also referred to as enhancers, are known. Upstream activation sequences for expression in *Saccharomyces cerevisiae* include, but are not limited to, the UASs of genes encoding the following proteins: PCK1, TPI, TDH3,

CYC1, ADH1, ADH2, SUC2, GAL1, GAL7 and GAL10, as well as other UASs activated by the GAL4 gene product, with the ADH2 UAS being used in one aspect. Since the ADH2 UAS is activated by the ADR1 gene product, it may be preferable to overexpress the ADR1 gene when a heterologous gene is operatively linked to the ADH2 UAS. Transcription termination sequences for expression in *Saccharomyces cerevisiae* include the termination sequences of the α -factor, GAPDH, and CYC1 genes.

Transcription control sequences to express genes in methy-

10 trophic yeast include the transcription control regions of the genes encoding alcohol oxidase and formate dehydrogenase. Transfection of a nucleic acid molecule into a yeast cell according to the present invention can be accomplished by any method by which a nucleic acid molecule can be intro-
15 duced into the cell and includes, but is not limited to, diffusion, active transport, bath sonication, electroporation, microinjection, lipofection, adsorption, and protoplast fusion. Transfected nucleic acid molecules can be integrated into a yeast chromosome or maintained on extrachromosomal
20 vectors using techniques known to those skilled in the art. Examples of yeast vehicles carrying such nucleic acid molecules are disclosed in detail herein. As discussed above, yeast cytoplasm, yeast ghost, and yeast membrane particles or cell wall preparations can also be produced recombinantly by
25 transfecting intact yeast microorganisms or yeast spheroplasts with desired nucleic acid molecules, producing the antigen therein, and then further manipulating the microor-
30 ganisms or spheroplasts using techniques known to those skilled in the art to produce cytoplasm, ghost or subcellular yeast membrane extract or fractions thereof containing desired antigens or other proteins.

Effective conditions for the production of recombinant yeast vehicles and expression of the antigen and/or other protein by the yeast vehicle include an effective medium in
35 which a yeast strain can be cultured. An effective medium is typically an aqueous medium comprising assimilable carbohydrate, nitrogen and phosphate sources, as well as appropriate salts, minerals, metals and other nutrients, such as vitamins and growth factors. The medium may comprise complex
40 nutrients or may be a defined minimal medium. Yeast strains of the present invention can be cultured in a variety of containers, including, but not limited to, bioreactors, Erlenmeyer flasks, test tubes, microtiter dishes, and Petri plates. Culturing is carried out at a temperature, pH and oxygen content appro-
45 priate for the yeast strain. Such culturing conditions are well within the expertise of one of ordinary skill in the art (see, for example, Guthrie et al. (eds.), 1991, Methods in Enzymology, vol. 194, Academic Press, San Diego).

In some aspects of the invention, the yeast are grown under
50 neutral pH conditions, and particularly, in a media maintained at a pH level of at least 5.5, namely the pH of the culture media is not allowed to drop below pH 5.5. In other aspects, the yeast is grown at a pH level maintained at about 5.5. In other
55 aspects, the yeast is grown at a pH level maintained at about 5.6, 5.7, 5.8 or 5.9. In another aspect, the yeast is grown at a pH level maintained at about 6. In another aspect, the yeast is grown at a pH level maintained at about 6.5. In other aspects, the yeast is grown at a pH level maintained at about 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9 or 7.0. In other aspects, the yeast
60 is grown at a pH level maintained at about 7, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, or 8.0. The pH level is important in the culturing of yeast. One of skill in the art will appreciate that the culturing process includes not only the start of the yeast culture but the maintenance of the culture as well. As yeast
65 culturing is known to turn acidic (i.e., lowering the pH) over time, care must be taken to monitor the pH level during the

culturing process. Yeast cell cultures whereby the pH level of the medium drops below 6 are still contemplated within the scope of the invention provided that the pH of the media is brought up to at least 5.5 at some point during the culturing
5 process. As such, the longer time the yeast are grown in a medium that is at least pH 5.5 or above, the better the results will be in terms of obtaining yeast with desirable characteristics.

As used herein, the general use of the term "neutral pH" refers to a pH range between about pH 5.5 and about pH 8, and in one aspect, between about pH 6 and about 8. One of skill the art will appreciate that minor fluctuations (e.g., tenths or hundredths) can occur when measuring with a pH meter. As
10 such, the use of neutral pH to grow yeast cells means that the yeast cells are grown in neutral pH for the majority of the time that they are in culture. The use of a neutral pH in culturing yeast promotes several biological effects that are desirable characteristics for using the yeast as vehicles for immuno-
15 modulation. In one aspect, culturing the yeast in neutral pH allows for good growth of the yeast without any negative effect on the cell generation time (e.g., slowing down the doubling time). The yeast can continue to grow to high densities without losing their cell wall pliability. In another aspect, the use of a neutral pH allows for the production of
20 yeast with pliable cell walls and/or yeast that are sensitive to cell wall digesting enzymes (e.g., glucanase) at all harvest densities. This trait is desirable because yeast with flexible cell walls can induce unusual immune responses, such as by promoting the secretion of cytokines (e.g., interferon- γ (IFN- γ)) in the cells hosting the yeast. In addition, greater accessi-
25 bility to the antigens located in the cell wall is afforded by such culture methods. In another aspect, the use of neutral pH for some antigens allows for release of the di-sulfide bonded antigen by treatment with dithiothreitol (DTT) that is not possible when such an antigen-expressing yeast is cultured in media at lower pH (e.g., pH 5). Finally, in another aspect, yeast cultured using the neutral pH methodologies, elicit increased production of at least TH1-type cytokines includ-
30 ing, but not limited to, IFN- γ , interleukin-12 (IL-12), and IL-2, and may also elicit increased production of other cytokines, such as proinflammatory cytokines (e.g., IL-6).

In one embodiment, control of the amount of yeast glyco-
35 sylation is used to control the expression of antigens by the yeast, particularly on the surface. The amount of yeast glycosylation can affect the immunogenicity and antigenicity of the antigen expressed on the surface, since sugar moieties tend to be bulky. As such, the existence of sugar moieties on the surface of yeast and its impact on the three-dimensional space around the target antigen(s) should be considered in the modulation of yeast according to the invention. Any method
40 can be used to reduce the amount of glycosylation of the yeast (or increase it, if desired). For example, one could use a yeast mutant strain that has been selected to have low glycosylation (e.g. *mn1*, *och1* and *mn9* mutants), or one could eliminate
45 by mutation the glycosylation acceptor sequences on the target antigen. Alternatively, one could use a yeast with abbreviated glycosylation patterns, e.g., *Pichia*. One can also treat the yeast using methods that reduce or alter the glycosylation.

In one embodiment of the present invention, as an alterna-
50 tive to expression of an antigen or other protein recombinantly in the yeast vehicle, a yeast vehicle is loaded intracellularly with the protein or peptide, or with carbohydrates or other molecules that serve as an antigen and/or are useful as immunomodulatory agents or biological response modifiers according to the invention. Subsequently, the yeast vehicle,
55 which now contains the antigen and/or other proteins intracellularly, can be administered to an individual or loaded into

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a carrier such as a dendritic cell. Peptides and proteins can be inserted directly into yeast vehicles of the present invention by techniques known to those skilled in the art, such as by diffusion, active transport, liposome fusion, electroporation, phagocytosis, freeze-thaw cycles and bath sonication. Yeast vehicles that can be directly loaded with peptides, proteins, carbohydrates, or other molecules include intact yeast, as well as spheroplasts, ghosts or cytoplasts, which can be loaded with antigens and other agents after production. Alternatively, intact yeast can be loaded with the antigen and/or agent, and then spheroplasts, ghosts, cytoplasts, or subcellular particles can be prepared therefrom. Any number of antigens and/or other agents can be loaded into a yeast vehicle in this embodiment, from at least 1, 2, 3, 4 or any whole integer up to hundreds or thousands of antigens and/or other agents, such as would be provided by the loading of a microorganism or portions thereof, for example.

In another embodiment of the present invention, an antigen and/or other agent is physically attached to the yeast vehicle. Physical attachment of the antigen and/or other agent to the yeast vehicle can be accomplished by any method suitable in the art, including covalent and non-covalent association methods which include, but are not limited to, chemically crosslinking the antigen and/or other agent to the outer surface of the yeast vehicle or biologically linking the antigen and/or other agent to the outer surface of the yeast vehicle, such as by using an antibody or other binding partner. Chemical cross-linking can be achieved, for example, by methods including glutaraldehyde linkage, photoaffinity labeling, treatment with carbodiimides, treatment with chemicals capable of linking di-sulfide bonds, and treatment with other cross-linking chemicals standard in the art. Alternatively, a chemical can be contacted with the yeast vehicle that alters the charge of the lipid bilayer of yeast membrane or the composition of the cell wall so that the outer surface of the yeast is more likely to fuse or bind to antigens and/or other agent having particular charge characteristics. Targeting agents such as antibodies, binding peptides, soluble receptors, and other ligands may also be incorporated into an antigen as a fusion protein or otherwise associated with an antigen for binding of the antigen to the yeast vehicle.

When the antigen or other protein is expressed on or physically attached to the surface of the yeast, spacer arms may, in one aspect, be carefully selected to optimize antigen or other protein expression or content on the surface. The size of the spacer arm(s) can affect how much of the antigen or other protein is exposed for binding on the surface of the yeast. Thus, depending on which antigen(s) or other protein(s) are being used, one of skill in the art will select a spacer arm that effectuates appropriate spacing for the antigen or other protein on the yeast surface. In one embodiment, the spacer arm is a yeast protein of at least 450 amino acids. Spacer arms have been discussed in detail above.

In yet another embodiment, the yeast vehicle and the antigen or other protein are associated with each other by a more passive, non-specific or non-covalent binding mechanism, such as by gently mixing the yeast vehicle and the antigen or other protein together in a buffer or other suitable formulation (e.g., admixture).

In one embodiment of the invention, the yeast vehicle and the antigen or other protein are both loaded intracellularly into a carrier such as a dendritic cell or macrophage to form the therapeutic composition or vaccine of the present invention. Alternatively, an antigen or other protein can be loaded into a dendritic cell in the absence of the yeast vehicle.

In one embodiment, intact yeast (with or without expression of heterologous antigens or other proteins) can be ground

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up or processed in a manner to produce yeast cell wall preparations, yeast membrane particles or yeast fragments (i.e., not intact) and the yeast fragments can, in some embodiments, be provided with or administered with other compositions that include antigens (e.g., DNA vaccines, protein subunit vaccines, killed or inactivated pathogens) to enhance immune responses. For example, enzymatic treatment, chemical treatment or physical force (e.g., mechanical shearing or sonication) can be used to break up the yeast into parts that are used as an adjuvant.

In one embodiment of the invention, yeast vehicles useful in the invention include yeast vehicles that have been killed or inactivated. Killing or inactivating of yeast can be accomplished by any of a variety of suitable methods known in the art. For example, heat inactivation of yeast is a standard way of inactivating yeast, and one of skill in the art can monitor the structural changes of the target antigen, if desired, by standard methods known in the art. Alternatively, other methods of inactivating the yeast can be used, such as chemical, electrical, radioactive or UV methods. See, for example, the methodology disclosed in standard yeast culturing textbooks such as *Methods of Enzymology*, Vol. 194, Cold Spring Harbor Publishing (1990). Any of the inactivation strategies used should take the secondary, tertiary or quaternary structure of the target antigen into consideration and preserve such structure as to optimize its immunogenicity.

Yeast vehicles can be formulated into yeast-based immunotherapy compositions or products of the present invention, including preparations to be administered to a subject directly or first loaded into a carrier such as a dendritic cell, using a number of techniques known to those skilled in the art. For example, yeast vehicles can be dried by lyophilization. Formulations comprising yeast vehicles can also be prepared by packing yeast in a cake or a tablet, such as is done for yeast used in baking or brewing operations. In addition, yeast vehicles can be mixed with a pharmaceutically acceptable excipient, such as an isotonic buffer that is tolerated by a host or host cell. Examples of such excipients include water, saline, Ringer's solution, dextrose solution, Hank's solution, and other aqueous physiologically balanced salt solutions. Nonaqueous vehicles, such as fixed oils, sesame oil, ethyl oleate, or triglycerides may also be used. Other useful formulations include suspensions containing viscosity-enhancing agents, such as sodium carboxymethylcellulose, sorbitol, glycerol or dextran. Excipients can also contain minor amounts of additives, such as substances that enhance isotonicity and chemical stability. Examples of buffers include phosphate buffer, bicarbonate buffer and Tris buffer, while examples of preservatives include thimerosal, m- or o-cresol, formalin and benzyl alcohol. Standard formulations can either be liquid injectables or solids which can be taken up in a suitable liquid as a suspension or solution for injection. Thus, in a non-liquid formulation, the excipient can comprise, for example, dextrose, human serum albumin, and/or preservatives to which sterile water or saline can be added prior to administration.

In one embodiment of the present invention, a composition can include additional agents, which may also be referred to as biological response modifier compounds, or the ability to produce such agents/modifiers. For example, a yeast vehicle can be transfected with or loaded with at least one antigen and at least one agent/biological response modifier compound, or a composition of the invention can be administered in conjunction with at least one agent/biological response modifier. Biological response modifiers include adjuvants and other compounds that can modulate immune responses, which may be referred to as immunomodulatory compounds, as well as

compounds that modify the biological activity of another compound or agent, such as a yeast-based immunotherapeutic, such biological activity not being limited to immune system effects. Certain immunomodulatory compounds can stimulate a protective immune response whereas others can suppress a harmful immune response, and whether an immunomodulatory is useful in combination with a given yeast-based immunotherapeutic may depend, at least in part, on the disease state or condition to be treated or prevented, and/or on the individual who is to be treated. Certain biological response modifiers preferentially enhance a cell-mediated immune response whereas others preferentially enhance a humoral immune response (i.e., can stimulate an immune response in which there is an increased level of cell-mediated compared to humoral immunity, or vice versa.). Certain biological response modifiers have one or more properties in common with the biological properties of yeast-based immunotherapeutics or enhance or complement the biological properties of yeast-based immunotherapeutics. There are a number of techniques known to those skilled in the art to measure stimulation or suppression of immune responses, as well as to differentiate cell-mediated immune responses from humoral immune responses, and to differentiate one type of cell-mediated response from another (e.g., a TH17 response versus a TH1 response).

Agents/biological response modifiers useful in the invention may include, but are not limited to, cytokines, chemokines, hormones, lipidic derivatives, peptides, proteins, polysaccharides, small molecule drugs, antibodies and antigen binding fragments thereof (including, but not limited to, anti-cytokine antibodies, anti-cytokine receptor antibodies, anti-chemokine antibodies), vitamins, polynucleotides, nucleic acid binding moieties, aptamers, and growth modulators. Some suitable agents include, but are not limited to, IL-1 or agonists of IL-1 or of IL-1R, anti-IL-1 or other IL-1 antagonists; IL-6 or agonists of IL-6 or of IL-6R, anti-IL-6 or other IL-6 antagonists; IL-12 or agonists of IL-12 or of IL-12R, anti-IL-12 or other IL-12 antagonists; IL-17 or agonists of IL-17 or of IL-17R, anti-IL-17 or other IL-17 antagonists; IL-21 or agonists of IL-21 or of IL-21R, anti-IL-21 or other IL-21 antagonists; IL-22 or agonists of IL-22 or of IL-22R, anti-IL-22 or other IL-22 antagonists; IL-23 or agonists of IL-23 or of IL-23R, anti-IL-23 or other IL-23 antagonists; IL-25 or agonists of IL-25 or of IL-25R, anti-IL-25 or other IL-25 antagonists; IL-27 or agonists of IL-27 or of IL-27R, anti-IL-27 or other IL-27 antagonists; type I interferon (including IFN- α) or agonists or antagonists of type I interferon or a receptor thereof; type II interferon (including IFN- γ) or agonists or antagonists of type II interferon or a receptor thereof; anti-CD40, CD40L, anti-CTLA-4 antibody (e.g., to release anergic T cells); T cell co-stimulators (e.g., anti-CD137, anti-CD28, anti-CD40); alemtuzumab (e.g., CAMPATH®), denileukin diftitox (e.g., ONTAK®); anti-CD4; anti-CD25; anti-PD-1, anti-PD-L1, anti-PD-L2; agents that block FOXP3 (e.g., to abrogate the activity/kill CD4⁺/CD25⁺ T regulatory cells); Flt3 ligand, imiquimod (ALDARA™), granulocyte-macrophage colony stimulating factor (GM-CSF); granulocyte-colony stimulating factor (G-CSF), sargramostim (Leukine®); hormones including without limitation prolactin and growth hormone; Toll-like receptor (TLR) agonists, including but not limited to TLR-2 agonists, TLR-4 agonists, TLR-7 agonists, and TLR-9 agonists; TLR antagonists, including but not limited to TLR-2 antagonists, TLR-4 antagonists, TLR-7 antagonists, and TLR-9 antagonists; anti-inflammatory agents and immunomodulators, including but not limited to, COX-2 inhibitors (e.g., Celecoxib, NSAIDS), glucocorticoids, statins, and tha-

lidomide and analogues thereof including IMiD™s (which are structural and functional analogues of thalidomide (e.g., REVLIMID® (lenalidomide), ACTIMID® (pomalidomide)); proinflammatory agents, such as fungal or bacterial components or any proinflammatory cytokine or chemokine; immunotherapeutic vaccines including, but not limited to, virus-based vaccines, bacteria-based vaccines, or antibody-based vaccines; and any other immunomodulators, immunopotentiators, anti-inflammatory agents, and/or pro-inflammatory agents. Any combination of such agents is contemplated by the invention, and any of such agents combined with or administered in a protocol with (e.g., concurrently, sequentially, or in other formats with) a yeast-based immunotherapeutic is a composition encompassed by the invention. Such agents are well known in the art. These agents may be used alone or in combination with other agents described herein.

Agents can include agonists and antagonists of a given protein or peptide or domain thereof. As used herein, an “agonist” is any compound or agent, including without limitation small molecules, proteins, peptides, antibodies, nucleic acid binding agents, etc., that binds to a receptor or ligand and produces or triggers a response, which may include agents that mimic the action of a naturally occurring substance that binds to the receptor or ligand. An “antagonist” is any compound or agent, including without limitation small molecules, proteins, peptides, antibodies, nucleic acid binding agents, etc., that blocks or inhibits or reduces the action of an agonist.

Compositions of the invention can further include or can be administered with (concurrently, sequentially, or intermittently with) any other compounds or compositions that are useful for preventing or treating Ad-36 infection or any compounds that treat or ameliorate any symptom of Ad-36 infection. In addition, compositions of the invention can be used together with other immunotherapeutic compositions, including prophylactic and/or therapeutic immunotherapy.

The invention also includes a kit comprising any of the compositions described herein, or any of the individual components of the compositions described herein. Kits may include additional reagents and written instructions or directions for using any of the compositions of the invention to prevent or treat Ad-36 infection and/or obesity or being overweight that is or may be associated with such an infection. Methods for Administration or Use of Compositions of the Invention

Compositions of the invention, which in one embodiment, include yeast-based immunotherapeutic compositions described above, as well as Ad-36 fusion proteins described herein and recombinant nucleic acid molecules encoding such Ad-36 fusion proteins, and other compositions comprising such yeast-based compositions, fusion proteins, or recombinant molecules described herein, can be used in a variety of in vivo and in vitro methods, including, but not limited to, methods and uses to treat and/or prevent Ad-36 infection and/or obesity, excess weight (e.g., being clinically overweight), or abnormal adipose tissue hypertrophy associated with Ad-36 infection, other symptoms and conditions associated with Ad-36 infection and/or excess weight or abnormal adipose tissue hypertrophy, in diagnostic assays for Ad-36, or to produce antibodies against Ad-36.

One embodiment of the invention relates to a method to treat Ad-36 infection, and/or to prevent, ameliorate or treat at least one symptom or sequela of chronic Ad-36 infection, in an individual or population of individuals. In one aspect, the invention relates to a method to reduce or prevent obesity, excess weight, or abnormal adipose tissue hypertrophy that is associated with Ad-36 infection, by reducing, halting, or preventing, Ad-36 infection. The method includes the step of

administering to an individual or a population of individuals who are, may be, or may become, infected with Ad-36, an immunotherapeutic composition of the invention. In one aspect, the composition is an immunotherapeutic composition comprising one or more Ad-36 antigens (Ad-36 proteins and/or immunogenic domains thereof), including any of the Ad-36 antigens (including any fusion protein) as described herein. In one aspect, the immunotherapeutic composition is a yeast-based immunotherapeutic composition. In one aspect, the composition includes a fusion protein comprising Ad-36 antigens as described herein, or recombinant nucleic acid molecule encoding such antigens. In one embodiment, the individual or population of individuals has Ad-36 infection (is currently infected with Ad-36 or at least has evidence of being infected). In one embodiment, the individual or population of individuals is overweight or obese, and in another embodiment, the individual or population of individuals is not overweight or is not obese. In one aspect, the individual or population of individuals is additionally treated with at least one other therapeutic compound or therapeutic protocol useful for the treatment of Ad-36 infection, or useful for the treatment of a condition associated with Ad-36 infection, including, but not limited to, obesity, being overweight, abnormal adipose tissue hypertrophy, type II diabetes, or symptoms of these conditions. Suitable additional therapeutic compounds include, but are not limited to, direct-acting antiviral drugs and/or interferons and/or other immunotherapeutic or immunomodulatory agents and/or insulin. Suitable additional therapeutic protocols include, but are not limited to, the administration of such agents, diet programs, and exercise programs.

Another embodiment of the invention relates to a method to immunize an individual or population of individuals against Ad-36 in order to prevent Ad-36 infection, prevent chronic Ad-36 infection, and/or reduce the severity of Ad-36 infection in the individual or population of individuals. The method includes the step of administering to an individual or population of individuals that is not infected with Ad-36 (or believed not to be infected with Ad-36 or not known to be or have been infected with Ad-36), a composition of the invention. In one aspect, the composition is an immunotherapeutic composition comprising one or more Ad-36 antigens as described herein, including a yeast-based immunotherapeutic composition. In one aspect, the composition includes a fusion protein comprising Ad-36 antigens as described herein, or recombinant nucleic acid molecule encoding such fusion protein.

As used herein, the phrase "treat" Ad-36 infection, or any permutation thereof (e.g., "treated for Ad-36 infection", etc.) generally refers to applying or administering a composition of the invention once the infection (acute or chronic) has occurred, with the goal of reduction or elimination of detectable viral titer, reaching seroconversion as measured by development of antibodies against Ad-36 that are reflective of an elimination of the virus, reduction in at least one symptom resulting from the infection in the individual (e.g., reduction in BMI, reduction in body weight, reduced rate of weight gain, reduced adiposity, etc.), delaying or preventing the onset and/or severity of symptoms and/or downstream sequela caused by the infection, reduction of organ or physiological system damage resulting from the infection, improvement in organ or system function that was negatively impacted by the infection, improvement of immune responses against the virus, improvement of long term memory immune responses against the virus, and/or improved general health of the individual or population of individuals. To "prevent" Ad-36 infection, or any permutation

thereof (e.g., "prevention of Ad-36 infection", etc.), generally refers to applying or administering a composition of the invention before an infection with Ad-36 has occurred, with the goal of preventing infection by Ad-36, preventing chronic infection by Ad-36 (i.e., enabling an individual to clear an acute Ad-36 infection without further intervention), or at least reducing the severity, and/or length of infection and/or the physiological damage caused by the chronic infection, and/or reducing the rate of weight gain, in an individual or population of individuals should the infection later occur.

According to the present invention, body mass index, or BMI, is routinely used to determine a degree of weight excess (e.g., being overweight) and obesity, although it is not a direct measure of body fat. It is a measure of weight in relation to height of an individual and can be calculated in English or metric units. According to the Centers for Disease Control and Prevention (CDC), an adult who has a body mass index (BMI) between 25 and 29.9 is considered to be overweight. An adult who has a BMI of 30 or higher is considered to be obese. For children and teens, BMI ranges above a normal weight have different labels and take into account normal differences in body fat between boys and girls and differences in body fat at various ages. Being "overweight" in children and teens ages 2-19 years is defined as a BMI at or above the 85th percentile and lower than the 95th percentile for children of the same age and sex. Obesity in children and teens ages 2-19 is defined as a BMI at or above the 95th percentile for children of the same age and sex. As used herein, the phrase "excess weight" is generally used to refer to a weight that is greater than that considered to be healthy for an individual of a given age, gender, and/or height, which is typically at least "overweight" as defined by the CDC or other public health institution and as set forth herein. Accordingly, the reference to "excess weight" can be used interchangeably with reference to "overweight" or "being overweight". BMI calculators for children and teens, as well as adults, are publicly available through the Centers for Disease Control and Prevention, for example, and can be used to determine BMI for a specific age, height, gender and weight (for children and teens, for adults, height and weight are considered), and advise the weight percentile for the individual if child or teen, and further advise whether the individual is considered to be potentially overweight or obese according to current standards for children, teens and adults.

According to the invention, reference to "abnormal adipose tissue", "hypertrophic adipose tissue" or "abnormal adipose tissue hypertrophy", refers to an increase in adipose tissue (adiposity) or adipocyte growth that is abnormal and typically presents as a benign lipoma or a deposit of adipose tissue in an unusual anatomical location. Abnormal adipose tissue is therefore distinguished from obesity, as an individual may not be clinically obese, but may have areas of abnormal adipose tissue or adipose tissue hypertrophy. Abnormal adipose tissue is, for example, a condition associated with HIV infection.

Preferably, the use of an immunotherapeutic composition of the invention results in the prevention of obesity or excess weight gain, in a reduction in weight gained or a reduced rate of weight gain in individuals who are or become infected with Ad-36, and/or in a reduction in the likelihood of becoming obese or overweight, in an individual who is or becomes infected with the virus but is not currently overweight or obese. In an adult individual with a BMI of 30 or higher, or in a child or teen aged 2-19 years with a BMI at or above the 95th percentile for children/teens of the same age and sex, in one aspect of the invention, the use of an immunotherapeutic composition of the invention results in a reduction of BMI in

the individual to less than 30 for such adults, or less than the 95th percentile for such children or teens. In an adult individual with a BMI of between 25 and 29.9, or in a child or teen aged 2-19 years with a BMI at or above the 85th percentile for children/teens of the same age and sex, in one aspect of the invention, the use of an immunotherapeutic composition of the invention results in a reduction of BMI to below 25 for such adults, and to less than the 85th percentile for such children or teen.

The efficacy, or effectiveness, of an immunotherapeutic composition of the invention can also be defined as a statistically significant change, or statistical trend, toward patient benefit in any one or more measurable or detectable parameter associated with Ad-36 infection or conditions linked to such infection, in an individual receiving the immunotherapeutic composition, as compared to a control value for the parameter being evaluated. In one aspect of the invention, a clinically relevant change can be measured as a percentage change toward patient benefit as compared to a prior evaluation, and can be 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, or greater. Benefit can also be measured as a change in the slope of a curve over time as compared to a control (e.g., a change in the slope of body weight or the rate of weight gain plotted over time before, during and after treatment).

Parameters to be evaluated for determination of effectiveness of a composition or method of the invention include, but are not limited to, viral load, viral clearance, adipose tissue hypertrophy, body weight, BMI, rate of weight gain, total body fat, serum cholesterol, triglycerides, blood pressure, glucose tolerance, insulin sensitivity, and immune responses, including Ad-36-specific T cell responses and neutralizing antibody responses. The control value can be selected from any suitable control value, including, but not limited to, one or more prior measurements of the parameter in the same individual; a measurement of the parameter as an average or mean in a population of individuals meeting similar criteria for gender, age, weight, and/or other clinical status; or a reference value provided in the form of stored information regarding a previously determined baseline level for the given parameter. Such a form of stored information can include, for example, but is not limited to, a reference chart, listing or electronic file of population or individual data regarding "healthy" individuals (negative control), or obese or overweight individuals or individuals infected with Ad-36 that have not been cured or treated (positive control); a medical chart for the individual recording data from previous evaluations; or any other source of data regarding baseline levels that are useful for the evaluation of the efficacy of the treatment.

According to the invention, a "baseline level" is a control level, and in some embodiments (but not all embodiments, depending on the method), a normal level, of a given clinical endpoint or parameter against which a test level of the given clinical endpoint or parameter can be compared. The term "negative control" used in reference to a baseline level of such a clinical endpoint or parameter typically refers to a baseline level established in a sample from the patient or from a population of individuals that is believed to be normal (i.e., not infected with Ad-36, not overweight, not obese, not being abnormal with respect to the endpoint being tested). In one embodiment, a baseline level or control can be established from an individual at the onset of therapeutic or preventative treatment so that the status of the individual can be monitored over time and/or so that the efficacy of a given therapeutic or prophylactic protocol can be evaluated over time (continuously or intermittently). A "positive control" can include any control that confirms the positive detection of the parameter

or clinical endpoint that is associated with Ad-36 infection and/or obesity or excess weight, or other associated endpoint.

Methods for detection of Ad-36 virus are known in the art and are described, for example, in WO 2007/120362, WO 2010 011440, WO 2007/064836, and WO 98/44946. The presence of viral DNA can be determined by conventional methods including, but not limited to, DNA sequencing, oligonucleotide hybridization, or PCR amplification. Detection of Ad-36 antibodies or proteins that bind to Ad-36 antibodies have also been described and such methods are encompassed by the invention. Binding can be measured using a variety of methods standard in the art, including, but not limited to: Western blot, immunoblot, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), immunoprecipitation, surface plasmon resonance, chemiluminescence, fluorescent polarization, phosphorescence, immunohistochemical analysis, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, microcytometry, microarray, microscopy, fluorescence activated cell sorting (FACS), and flow cytometry.

The present invention includes the delivery (administration, immunization) of an immunotherapeutic composition of the invention, including a yeast-based immunotherapy composition, to a subject. The administration process can be performed ex vivo or in vivo, but is typically performed in vivo. Ex vivo administration refers to performing part of the regulatory step outside of the patient, such as administering a composition of the present invention to a population of cells (dendritic cells) removed from a patient under conditions such that a yeast vehicle, antigen(s) and any other agents or compositions are loaded into the cell, and returning the cells to the patient. The therapeutic composition of the present invention can be returned to a patient, or administered to a patient, by any suitable mode of administration.

Administration of a composition can be systemic, mucosal and/or proximal to the location of the target site (e.g., near a site of infection or target tissue, such as adipose tissue). Suitable routes of administration will be apparent to those of skill in the art, depending on the type of condition to be prevented or treated, the antigen used, and/or the target cell population or tissue. Various acceptable methods of administration include, but are not limited to, intravenous administration, intraperitoneal administration, intramuscular administration, intranodal administration, intracoronary administration, intraarterial administration (e.g., into a carotid artery), subcutaneous administration, transdermal delivery, intratracheal administration, intraarticular administration, intraventricular administration, inhalation (e.g., aerosol), intracranial, intraspinal, intraocular, aural, intranasal, oral, pulmonary administration, impregnation of a catheter, and direct injection into a tissue. In one aspect, routes of administration include: intravenous, intraperitoneal, subcutaneous, intradermal, intranodal, intramuscular, transdermal, inhaled, intranasal, oral, intraocular, intraarticular, intracranial, and intraspinal. Parenteral delivery can include intradermal, intramuscular, intraperitoneal, intrapleural, intrapulmonary, intravenous, subcutaneous, atrial catheter and venal catheter routes. Aural delivery can include ear drops, intranasal delivery can include nose drops or intranasal injection, and intraocular delivery can include eye drops. Aerosol (inhalation) delivery can also be performed using methods standard in the art (see, for example, Stribling et al., *Proc. Natl. Acad. Sci. USA* 189:11277-11281, 1992). Other routes of administration that modulate mucosal immunity may be useful in the treatment of viral infections. Such routes include bronchial, intradermal, intramuscular, intranasal, other inhalatory, rectal, subcutaneous, topical, transdermal, vaginal and urethral

routes. In one aspect, an immunotherapeutic composition of the invention is administered subcutaneously. In one aspect, the immunotherapeutic composition is administered directly to adipose tissue.

With respect to the yeast-based immunotherapy compositions of the invention, in general, a suitable single dose is a dose that is capable of effectively providing a yeast vehicle and an antigen (if included) to a given cell type, tissue, or region of the patient body in an amount effective to elicit an antigen-specific immune response against one or more Ad-36 antigens or epitopes, when administered one or more times over a suitable time period. For example, in one embodiment, a single dose of a yeast vehicle of the present invention is from about 1×10^5 to about 5×10^7 yeast cell equivalents per kilogram body weight of the organism being administered the composition. In one aspect, a single dose of a yeast vehicle of the present invention is from about 0.1 Y.U. (1×10^6 cells) to about 100 Y.U. (1×10^9 cells) per dose (i.e., per organism), including any interim dose, in increments of 0.1×10^6 cells (i.e., 1.1×10^6 , 1.2×10^6 , 1.3×10^6 . . .). In one embodiment, doses include doses between 1 Y.U. and 40 Y.U. or 80 Y.U. and in one aspect, between 10 Y.U. and 40 Y.U. or 80 Y.U. In one embodiment, the doses are administered at different sites on the individual but during the same dosing period. For example, a 40 Y.U. dose may be administered via by injecting 10 Y.U. doses to four different sites on the individual during one dosing period, or a 20 Y.U. dose may be administered by injecting 5 Y.U. doses to four different sites on the individual, or by injecting 10 Y.U. doses to two different sites on the individual, during the same dosing period. The invention includes administration of an amount of the yeast-based immunotherapy composition (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 Y.U. or more) at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more different sites on an individual to form a single dose. One Yeast Unit (Y.U.) is 1×10^7 yeast cells.

“Boosters” or “boosts” of a therapeutic composition are administered, for example, when the immune response against the antigen has waned or as needed to provide an immune response or induce a memory response against a particular antigen or antigen(s). Boosters can be administered from about 1, 2, 3, 4, 5, 6, 7, or 8 weeks apart, to monthly, to bimonthly, to quarterly, to annually, to several years after the original administration. In one embodiment, an administration schedule is one in which from about 1×10^5 to about 5×10^7 yeast cell equivalents of a composition per kg body weight of the organism is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more times over a time period of from weeks, to months, to years. In one embodiment, the doses are administered weekly for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more doses, followed by monthly doses as needed to achieve the desired inhibition or elimination of the Ad-36 virus.

In one aspect of the invention, one or more additional therapeutic agents are administered sequentially with the yeast-based immunotherapy composition (e.g., a direct-acting antiviral, a nutraceutical composition, or the like). In another embodiment, one or more additional therapeutic agents are administered before the yeast-based immunotherapy composition is administered. In another embodiment, one or more additional therapeutic agents are administered after the yeast-based immunotherapy composition is administered. In one embodiment, one or more additional therapeutic agents are administered in alternating doses with the yeast-based immunotherapy composition, or in a protocol in which the yeast-based composition is administered at prescribed intervals in between or with one or more consecutive doses of the additional agents, or vice versa. In one embodiment, the yeast-based immunotherapy composition is administered in

one or more doses over a period of time prior to commencing the administration of the additional agents. In other words, the yeast-based immunotherapeutic composition is administered as a monotherapy for a period of time, and then the agent administration is added, either concurrently with new doses of yeast-based immunotherapy, or in an alternating fashion with yeast-based immunotherapy. Alternatively, the agent may be administered for a period of time prior to beginning administration of the yeast-based immunotherapy composition. In one aspect, the yeast is engineered to express or carry the agent, or a different yeast is engineered or produced to express or carry the agent.

In the method of the present invention, compositions and therapeutic compositions can be administered to animal, including any vertebrate, and particularly to any member of the Vertebrate class, *Mammalia*, including, without limitation, primates, rodents, livestock and domestic pets. Livestock include mammals to be consumed or that produce useful products (e.g., sheep for wool production). Mammals to treat or protect include humans, dogs, cats, mice, rats, goats, sheep, cattle, horses and pigs.

An “individual” is a vertebrate, such as a mammal, including without limitation a human. Mammals include, but are not limited to, farm animals, sport animals, pets, primates, mice and rats. The term “individual” can be used interchangeably with the term “animal”, “subject” or “patient”.

General Techniques Useful in the Invention

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry, nucleic acid chemistry, and immunology, which are well known to those skilled in the art. Such techniques are explained fully in the literature, such as, *Methods of Enzymology*, Vol. 194, Guthrie et al., eds., Cold Spring Harbor Laboratory Press (1990); *Biology and activities of yeasts*, Skinner, et al., eds., Academic Press (1980); *Methods in yeast genetics: a laboratory course manual*, Rose et al., Cold Spring Harbor Laboratory Press (1990); *The Yeast Saccharomyces: Cell Cycle and Cell Biology*, Pringle et al., eds., Cold Spring Harbor Laboratory Press (1997); *The Yeast Saccharomyces Gene Expression*, Jones et al., eds., Cold Spring Harbor Laboratory Press (1993); *The Yeast Saccharomyces: Genome Dynamics, Protein Synthesis, and Energetics*, Broach et al., eds., Cold Spring Harbor Laboratory Press (1992); *Molecular Cloning: A Laboratory Manual*, second edition (Sambrook et al., 1989) and *Molecular Cloning: A Laboratory Manual*, third edition (Sambrook and Russell, 2001), (jointly referred to herein as “Sambrook”); Current Protocols in Molecular Biology (F. M. Ausubel et al., eds., 1987, including supplements through 2001); *PCR: The Polymerase Chain Reaction*, (Mullis et al., eds., 1994); Harlow and Lane (1988), *Antibodies, A Laboratory Manual*, Cold Spring Harbor Publications, New York; Harlow and Lane (1999) *Using Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (jointly referred to herein as “Harlow and Lane”); Beaucage et al. eds., *Current Protocols in Nucleic Acid Chemistry*, John Wiley & Sons, Inc., New York, 2000; Casarett and Doull’s *Toxicology The Basic Science of Poisons*, C. Klaassen, ed., 6th edition (2001), and *Vaccines*, S. Plotkin, W. Orenstein, and P. Offit, eds., Fifth Edition (2008).

GENERAL DEFINITIONS

As used herein, the term “analog” refers to a chemical compound that is structurally similar to another compound but differs slightly in composition (as in the replacement of

one atom by an atom of a different element or in the presence of a particular functional group, or the replacement of one functional group by another functional group). Thus, an analog is a compound that is similar or comparable in function and appearance, but has a different structure or origin with respect to the reference compound.

The terms “substituted”, “substituted derivative” and “derivative”, when used to describe a compound, means that at least one hydrogen bound to the unsubstituted compound is replaced with a different atom or a chemical moiety.

Although a derivative has a similar physical structure to the parent compound, the derivative may have different chemical and/or biological properties than the parent compound. Such properties can include, but are not limited to, increased or decreased activity of the parent compound, new activity as compared to the parent compound, enhanced or decreased bioavailability, enhanced or decreased efficacy, enhanced or decreased stability in vitro and/or in vivo, and/or enhanced or decreased absorption properties.

In general, the term “biologically active” indicates that a compound (including a protein or peptide) has at least one detectable activity that has an effect on the metabolic or other processes of a cell or organism, as measured or observed in vivo (i.e., in a natural physiological environment) or in vitro (i.e., under laboratory conditions).

According to the present invention, the term “modulate” can be used interchangeably with “regulate” and refers generally to upregulation or downregulation of a particular activity. As used herein, the term “upregulate” can be used generally to describe any of: elicitation, initiation, increasing, augmenting, boosting, improving, enhancing, amplifying, promoting, or providing, with respect to a particular activity. Similarly, the term “downregulate” can be used generally to describe any of: decreasing, reducing, inhibiting, ameliorating, diminishing, lessening, blocking, or preventing, with respect to a particular activity.

In one embodiment of the present invention, any of the amino acid sequences described herein can be produced with from at least one, and up to about 20, additional heterologous amino acids flanking each of the C- and/or N-terminal ends of the specified amino acid sequence. The resulting protein or polypeptide can be referred to as “consisting essentially of” the specified amino acid sequence. According to the present invention, the heterologous amino acids are a sequence of amino acids that are not naturally found (i.e., not found in nature, in vivo) flanking the specified amino acid sequence, or that are not related to the function of the specified amino acid sequence, or that would not be encoded by the nucleotides that flank the naturally occurring nucleic acid sequence encoding the specified amino acid sequence as it occurs in the gene, if such nucleotides in the naturally occurring sequence were translated using standard codon usage for the organism from which the given amino acid sequence is derived. Similarly, the phrase “consisting essentially of”, when used with reference to a nucleic acid sequence herein, refers to a nucleic acid sequence encoding a specified amino acid sequence that can be flanked by from at least one, and up to as many as about 60, additional heterologous nucleotides at each of the 5' and/or the 3' end of the nucleic acid sequence encoding the specified amino acid sequence. The heterologous nucleotides are not naturally found (i.e., not found in nature, in vivo) flanking the nucleic acid sequence encoding the specified amino acid sequence as it occurs in the natural gene or do not encode a protein that imparts any additional function to the protein or changes the function of the protein having the specified amino acid sequence.

According to the present invention, the phrase “selectively binds to” refers to the ability of an antibody, antigen-binding fragment or binding partner of the present invention to preferentially bind to specified proteins. More specifically, the phrase “selectively binds” refers to the specific binding of one protein to another (e.g., an antibody, fragment thereof, or binding partner to an antigen), wherein the level of binding, as measured by any standard assay (e.g., an immunoassay), is statistically significantly higher than the background control for the assay. For example, when performing an immunoassay, controls typically include a reaction well/tube that contain antibody or antigen binding fragment alone (i.e., in the absence of antigen), wherein an amount of reactivity (e.g., non-specific binding to the well) by the antibody or antigen-binding fragment thereof in the absence of the antigen is considered to be background. Binding can be measured using a variety of methods standard in the art including enzyme immunoassays (e.g., ELISA, immunoblot assays, etc.).

Reference to a protein or polypeptide used in the present invention includes full-length proteins, fusion proteins, or any fragment, domain (structural, functional, or immunogenic), conformational epitope, or homologue of such proteins. An isolated protein, according to the present invention, is a protein (including a polypeptide or peptide) that has been removed from its natural milieu (i.e., that has been subject to human manipulation) and can include purified proteins, partially purified proteins, recombinantly produced proteins, and synthetically produced proteins, for example. As such, “isolated” does not reflect the extent to which the protein has been purified. Preferably, an isolated protein of the present invention is produced recombinantly. According to the present invention, the terms “modification” and “mutation” can be used interchangeably, particularly with regard to the modifications/mutations to the amino acid sequence of proteins or portions thereof (or nucleic acid sequences) described herein.

As used herein, the term “homologue” is used to refer to a protein or peptide which differs from a naturally occurring protein or peptide (i.e., the “prototype” or “wild-type” protein) by minor modifications to the naturally occurring protein or peptide, but which maintains the basic protein and side chain structure of the naturally occurring form. Such changes include, but are not limited to: changes in one or a few amino acid side chains; changes one or a few amino acids, including deletions (e.g., a truncated version of the protein or peptide) insertions and/or substitutions; changes in stereochemistry of one or a few atoms; and/or minor derivatizations, including but not limited to: methylation, glycosylation, phosphorylation, acetylation, myristoylation, prenylation, palmitation, amidation and/or addition of glycosylphosphatidyl inositol. A homologue can have either enhanced, decreased, or substantially similar properties as compared to the naturally occurring protein or peptide. A homologue can include an agonist of a protein or an antagonist of a protein. Homologues can be produced using techniques known in the art for the production of proteins including, but not limited to, direct modifications to the isolated, naturally occurring protein, direct protein synthesis, or modifications to the nucleic acid sequence encoding the protein using, for example, classic or recombinant DNA techniques to effect random or targeted mutagenesis.

A homologue of a given protein may comprise, consist essentially of, or consist of, an amino acid sequence that is at least about 45%, or at least about 50%, or at least about 55%, or at least about 60%, or at least about 65%, or at least about 70%, or at least about 75%, or at least about 80%, or at least about 85%, or at least about 90%, or at least about 95% identical, or at least about 95% identical, or at least about 96%

identical, or at least about 97% identical, or at least about 98% identical, or at least about 99% identical (or any percent identity between 45% and 99%, in whole integer increments), to the amino acid sequence of the reference protein. In one embodiment, the homologue comprises, consists essentially of, or consists of, an amino acid sequence that is less than 100% identical, less than about 99% identical, less than about 98% identical, less than about 97% identical, less than about 96% identical, less than about 95% identical, and so on, in increments of 1%, to less than about 70% identical to the naturally occurring amino acid sequence of the reference protein.

As used herein, unless otherwise specified, reference to a percent (%) identity refers to an evaluation of homology which is performed using: (1) a BLAST 2.0 Basic BLAST homology search using blastp for amino acid searches and blastn for nucleic acid searches with standard default parameters, wherein the query sequence is filtered for low complexity regions by default (described in Altschul, S. F., Madden, T. L., Schääffer, A. A., Zhang, J., Zhang, Z., Miller, W. & Lipman, D. J. (1997) "Gapped BLAST and PSI-BLAST: a new generation of protein database search programs." *Nucleic Acids Res.* 25:3389-3402, incorporated herein by reference in its entirety); (2) a BLAST 2 alignment (using the parameters described below); (3) and/or PSI-BLAST with the standard default parameters (Position-Specific Iterated BLAST. It is noted that due to some differences in the standard parameters between BLAST 2.0 Basic BLAST and BLAST 2, two specific sequences might be recognized as having significant homology using the BLAST 2 program, whereas a search performed in BLAST 2.0 Basic BLAST using one of the sequences as the query sequence may not identify the second sequence in the top matches. In addition, PSI-BLAST provides an automated, easy-to-use version of a "profile" search, which is a sensitive way to look for sequence homologues. The program first performs a gapped BLAST database search. The PSI-BLAST program uses the information from any significant alignments returned to construct a position-specific score matrix, which replaces the query sequence for the next round of database searching. Therefore, it is to be understood that percent identity can be determined by using any one of these programs.

Two specific sequences can be aligned to one another using BLAST 2 sequence as described in Tatusova and Madden, (1999), "Blast 2 sequences—a new tool for comparing protein and nucleotide sequences", *FEMS Microbiol Lett.* 174: 247-250, incorporated herein by reference in its entirety. BLAST 2 sequence alignment is performed in blastp or blastn using the BLAST 2.0 algorithm to perform a Gapped BLAST search (BLAST 2.0) between the two sequences allowing for the introduction of gaps (deletions and insertions) in the resulting alignment. For purposes of clarity herein, a BLAST 2 sequence alignment is performed using the standard default parameters as follows.

For blastn, using 0 BLOSUM62 matrix:

Reward for match=1

Penalty for mismatch=-2

Open gap (5) and extension gap (2) penalties

gap x_dropoff (50) expect (10) word size (11) filter (on)

For blastp, using 0 BLOSUM62 matrix:

Open gap (11) and extension gap (1) penalties

gap x_dropoff (50) expect (10) word size (3) filter (on).

An isolated nucleic acid molecule is a nucleic acid molecule that has been removed from its natural milieu (i.e., that has been subject to human manipulation), its natural milieu being the genome or chromosome in which the nucleic acid molecule is found in nature. As such, "isolated" does not

necessarily reflect the extent to which the nucleic acid molecule has been purified, but indicates that the molecule does not include an entire genome or an entire chromosome in which the nucleic acid molecule is found in nature. An isolated nucleic acid molecule can include a gene. An isolated nucleic acid molecule that includes a gene is not a fragment of a chromosome that includes such gene, but rather includes the coding region and regulatory regions associated with the gene, but no additional genes that are naturally found on the same chromosome. An isolated nucleic acid molecule may also include portions of a gene. An isolated nucleic acid molecule can also include a specified nucleic acid sequence flanked by (i.e., at the 5' and/or the 3' end of the sequence) additional nucleic acids that do not normally flank the specified nucleic acid sequence in nature (i.e., heterologous sequences). Isolated nucleic acid molecule can include DNA, RNA (e.g., mRNA), or derivatives of either DNA or RNA (e.g., cDNA). Although the phrase "nucleic acid molecule" primarily refers to the physical nucleic acid molecule and the phrase "nucleic acid sequence" primarily refers to the sequence of nucleotides on the nucleic acid molecule, the two phrases can be used interchangeably, especially with respect to a nucleic acid molecule, or a nucleic acid sequence, being capable of encoding a protein or domain of a protein.

A recombinant nucleic acid molecule is a molecule that can include at least one of any nucleic acid sequence encoding any one or more proteins described herein operatively linked to at least one of any transcription control sequence capable of effectively regulating expression of the nucleic acid molecule(s) in the cell to be transfected. Although the phrase "nucleic acid molecule" primarily refers to the physical nucleic acid molecule and the phrase "nucleic acid sequence" primarily refers to the sequence of nucleotides on the nucleic acid molecule, the two phrases can be used interchangeably, especially with respect to a nucleic acid molecule, or a nucleic acid sequence, being capable of encoding a protein. In addition, the phrase "recombinant molecule" primarily refers to a nucleic acid molecule operatively linked to a transcription control sequence, but can be used interchangeably with the phrase "nucleic acid molecule" which is administered to an animal.

A recombinant nucleic acid molecule includes a recombinant vector, which is any nucleic acid sequence, typically a heterologous sequence, which is operatively linked to the isolated nucleic acid molecule encoding a fusion protein of the present invention, which is capable of enabling recombinant production of the fusion protein, and which is capable of delivering the nucleic acid molecule into a host cell according to the present invention. Such a vector can contain nucleic acid sequences that are not naturally found adjacent to the isolated nucleic acid molecules to be inserted into the vector. The vector can be either RNA or DNA, either prokaryotic or eukaryotic, and preferably in the present invention, is a virus or a plasmid. Recombinant vectors can be used in the cloning, sequencing, and/or otherwise manipulating of nucleic acid molecules, and can be used in delivery of such molecules (e.g., as in a DNA composition or a viral vector-based composition). Recombinant vectors are preferably used in the expression of nucleic acid molecules, and can also be referred to as expression vectors. Preferred recombinant vectors are capable of being expressed in a transfected host cell.

In a recombinant molecule of the present invention, nucleic acid molecules are operatively linked to expression vectors containing regulatory sequences such as transcription control sequences, translation control sequences, origins of replication, and other regulatory sequences that are compatible with the host cell and that control the expression of nucleic acid

molecules of the present invention. In particular, recombinant molecules of the present invention include nucleic acid molecules that are operatively linked to one or more expression control sequences. The phrase “operatively linked” refers to linking a nucleic acid molecule to an expression control sequence in a manner such that the molecule is expressed when transfected (i.e., transformed, transduced or transfected) into a host cell.

According to the present invention, the term “transfection” is used to refer to any method by which an exogenous nucleic acid molecule (i.e., a recombinant nucleic acid molecule) can be inserted into a cell. The term “transformation” can be used interchangeably with the term “transfection” when such term is used to refer to the introduction of nucleic acid molecules into microbial cells, such as algae, bacteria and yeast. In microbial systems, the term “transformation” is used to describe an inherited change due to the acquisition of exogenous nucleic acids by the microorganism and is essentially synonymous with the term “transfection.” Therefore, transfection techniques include, but are not limited to, transformation, chemical treatment of cells, particle bombardment, electroporation, microinjection, lipofection, adsorption, infection and protoplast fusion.

The following experimental results are provided for purposes of illustration and are not intended to limit the scope of the invention.

EXAMPLES

Example 1

Yeast-Based Immunotherapeutic Design and Production

The following example describes the design and production of several different yeast-based immunotherapeutic compositions for the treatment or prevention of adenovirus-36 (Ad-36) infection.

In these experiments, yeast (e.g., *Saccharomyces cerevisiae*) were engineered to express various Ad-36 fusion proteins under the control of the copper-inducible promoter, CUP1, or the TEF2 promoter. Briefly, to produce each of the yeast-based immunotherapeutics constructed in this Example, DNA encoding the Ad-36 antigen as set forth for each fusion protein below was prepared, codon optimized for expression in yeast, and then digested with SpeI and NotI and inserted behind the CUP1 promoter (pGI-100) or the TEF2 promoter (pTK57-1), as indicated for each construct below, in yeast 2 μ m expression vectors. The resulting plasmids were introduced into *Saccharomyces cerevisiae* W303 α yeast by Lithium acetate/polyethylene glycol transfection, and primary transfectants were selected on solid minimal plates lacking Uracil (UDM; uridine dropout medium). Other yeast strains, yeast species or yeast genera can be used in yeast-based immunotherapeutics of the invention; *Saccharomyces cerevisiae* W303 α is an exemplary strain. Colonies were restreaked onto UDM or ULDM (uridine and leucine dropout medium) and allowed to grow for 3 days at 30° C. Liquid cultures lacking uridine (U2) or lacking uridine and leucine (UL2) were inoculated from plates and starter cultures were grown for 20 h at 30° C., 250 rpm. If desired, although not used for these experiments, pH buffered media containing 4.2 g/L of Bis-Tris (BT-U2; BT-UL2) can be inoculated. Primary cultures were used to inoculate final cultures of the same formulation and growth is continued until a density of 1.1 to 4.0 Y.U./mL is reached.

For TEF2 strains (constitutive expression), cells were then harvested, washed and heat killed at 56° C. for 1 h in PBS. For CUP1 strains (inducible expression), expression was induced in the same medium with 0.375 mM copper sulfate for 5 h at 30° C., 250 rpm. Cells were harvested, washed and heat killed at 56° C. for 1 h in PBS.

After heat kill of TEF2 and CUP1 cultures, cells were washed three times in PBS. Total protein expression was measured by a TCA precipitation/nitrocellulose binding assay and Ad-36 fusion protein expression was measured by western blot using an anti-his tag monoclonal antibody (see FIGS. 1 and 2). As described below, FIGS. 1 and 2 showed that the yeast-based immunotherapy composition of the invention expressed the Ad-36 fusion protein well using both promoters, and using two different N-terminal sequences in the fusion proteins (SEQ ID NO:56 or SEQ ID NO:58), and were readily identified by Western blot.

Recipe for U2 liquid medium:

20 g/L of glucose
6.7 g/L of Yeast nitrogen base containing ammonium sulfate
0.04 mg/mL each of histidine, leucine, tryptophan, and adenine

Recipe for UL2 liquid medium:

20 g/L of glucose
6.7 g/L of Yeast nitrogen base containing ammonium sulfate
0.04 mg/mL each of histidine, tryptophan, and adenine

Several different yeast-based immunotherapeutics expressing Ad-36 fusion proteins were produced in this experiment. One yeast-based immunotherapeutic, denoted in FIG. 1 as “FIB”, was designed to express an Ad-36 fusion protein as a single polypeptide comprising selected portions of the Ad-36 fiber protein (the full Ad-36 fiber protein is represented by SEQ ID NO:34), fused at its N-terminus to a synthetic peptide represented by SEQ ID NO:58. *Saccharomyces cerevisiae* were engineered to express this protein under the control of the TEF2 promoter. The fusion protein has the following sequence elements fused in frame from N- to C-terminus, represented by SEQ ID NO:42: (1) an N-terminal peptide to impart resistance to proteasomal degradation and stabilize expression (positions 1 to 6 of SEQ ID NO:42); (2) positions 71-136 of Ad-36 fiber (positions 71-136 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 7-72 of SEQ ID NO:42; (3) positions 145-169 of Ad-36 fiber (positions 145-169 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 73-97 of SEQ ID NO:42; (4) positions 290-313 of Ad-36 fiber (positions 290-313 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 98-194 of SEQ ID NO:42; (5) positions 334-363 of Ad-36 fiber (positions 334-363 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 195-224 of SEQ ID NO:42; and (6) a hexahistidine tag (positions 225-230 of SEQ ID NO:42). The amino acid segments used in this fusion protein can be modified by the use of additional amino acids flanking either end of any domain. The nucleic acid sequence encoding the fusion protein of SEQ ID NO:42 was codon optimized for expression in yeast, and the yeast-based immunotherapeutic expressing this fusion protein was produced as described above.

The expression of this Ad-36 fiber fusion protein in yeast is shown in FIG. 1 (FIB). The estimated expression level of the fusion protein was 1704 ng/Y.U.

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Another yeast-based immunotherapeutic, denoted in FIG. 2 as “aFL-Fib” was designed to express an Ad-36 fusion protein as a single polypeptide comprising portions of the Ad-36 fiber protein (the full Ad-36 fiber protein is represented by SEQ ID NO:34) fused at its N-terminus to a yeast alpha factor signal leader (SEQ ID NO:56). *Saccharomyces cerevisiae* were engineered to express this protein under the control of the CUP1 promoter. This fusion protein has the following sequence elements fused in frame from N- to C-terminus, represented by SEQ ID NO:48: (1) an N-terminal peptide to impart resistance to proteasomal degradation and stabilize or enhance expression (SEQ ID NO:56, or positions 1 to 89 of SEQ ID NO: 48); (2) a two amino acid spacer/linker (Thr-Ser) to facilitate cloning and manipulation of the sequences (positions 90 to 91 of SEQ ID NO:48); (3) positions 71-136 of Ad-36 fiber (positions 71-136 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 92-157 of SEQ ID NO:48; (4) positions 145-169 of Ad-36 fiber (positions 145-169 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 158-182 of SEQ ID NO:48; (5) positions 290-313 of Ad-36 fiber (positions 290-313 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 183-279 of SEQ ID NO:48; (6) positions 334-363 of Ad-36 fiber (positions 334-363 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 280-309 of SEQ ID NO:48; and (7) a hexahistidine tag (positions 310-315 of SEQ ID NO:48). The amino acid segments used in this fusion protein can be modified by the use of additional amino acids flanking either end of any domain; the example provided herein is exemplary. The nucleic acid sequence encoding the fusion protein of SEQ ID NO:48 was codon optimized for expression in yeast, and the yeast-based immunotherapeutic expressing this fusion protein was produced as described above.

The expression of this Ad-36 fiber fusion protein in yeast is shown in FIG. 2 (aFL-FIB). The estimated expression level of the fusion protein was 14,854 ng/Y.U.

Another yeast-based immunotherapeutic, denoted in FIG. 1 as “HEX”, was designed to express an Ad-36 fusion protein as a single polypeptide comprising portions of the Ad-36 hexon protein (the full Ad-36 hexon protein is represented by SEQ ID NO:18) fused at its N-terminus to a synthetic peptide represented by SEQ ID NO:58. *Saccharomyces cerevisiae* were engineered to express this protein under the control of the TEF2 promoter. This fusion protein has the following sequence elements fused in frame from N- to C-terminus, represented by SEQ ID NO:43: (1) an N-terminal peptide to impart resistance to proteasomal degradation and stabilize expression (positions 1 to 6 of SEQ ID NO:43); (2) positions 136-218 of Ad-36 hexon (positions 136-218 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 7-89 of SEQ ID NO:43; (3) positions 235-285 of Ad-36 hexon (positions 235-285 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 90-141 of SEQ ID NO:43; (4) positions 297-308 of Ad-36 hexon (positions 297-308 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 142-153 of SEQ ID NO:43; (5) positions 410-450 of Ad-36 hexon (positions 410-450 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 154-194 of SEQ ID NO:43; and (6) a hexahistidine tag (positions 195-200 of SEQ ID NO:43). The amino acid segments used in this fusion protein can be modified by the use of additional amino acids

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flanking either end of any domain. The nucleic acid sequence encoding the fusion protein of SEQ ID NO:43 was codon optimized for expression in yeast, and the yeast-based immunotherapeutic expressing this fusion protein was produced as described above.

The expression of this Ad-36 hexon fusion protein in yeast is shown in FIG. 1 (HEX). The estimated expression level of this protein was 1981 ng/Y.U.

Another yeast-based immunotherapeutic, denoted in FIG. 2 as “aFL-Hexon” was designed to express an Ad-36 fusion protein as a single polypeptide comprising portions of the Ad-36 hexon protein (the full Ad-36 hexon protein is represented by SEQ ID NO:18) fused with yeast alpha factor leader signal sequence (SEQ ID NO:56). *Saccharomyces cerevisiae* were engineered to express this protein under the control of the CUP1 promoter. This fusion protein has the following sequence elements fused in frame from N- to C-terminus, represented by SEQ ID NO:50: (1) an N-terminal peptide to impart resistance to proteasomal degradation and stabilize or enhance expression (SEQ ID NO:56, or positions 1 to 89 of SEQ ID NO:50); (2) a two amino acid spacer/linker (Thr-Ser) to facilitate cloning and manipulation of the sequences (positions 90 to 91 of SEQ ID NO:50); (3) positions 136-218 of Ad-36 hexon (positions 136-218 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 92-174 of SEQ ID NO:50; (4) positions 235-285 of Ad-36 hexon (positions 235-285 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 175-226 of SEQ ID NO:50; (5) positions 297-308 of Ad-36 hexon (positions 297-308 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 227-238 of SEQ ID NO:50; (6) positions 410-450 of Ad-36 hexon (positions 410-450 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 239-279 of SEQ ID NO:50; and (7) a hexahistidine tag (positions 280-285 of SEQ ID NO:50). The amino acid segments used in this fusion protein can be modified by the use of additional amino acids flanking either end of any domain. The nucleic acid sequence encoding the fusion protein of SEQ ID NO:50 was codon optimized for expression in yeast, and the yeast-based immunotherapeutic expressing this fusion protein was produced as described above.

The expression of this Ad-36 hexon fusion protein in yeast is shown in FIG. 2 (aFL-Hexon). The estimated expression level of this protein was 19,695 ng/Y.U.

Another yeast-based immunotherapeutic, denoted in FIG. 2 as “aFL-Hexon-F”, was designed to express an Ad-36 fusion protein as a single polypeptide comprising the full-length Ad-36 hexon protein (the full hexon protein is represented by SEQ ID NO:18), fused at its N-terminus to yeast alpha factor leader sequence (SEQ ID NO:56). *Saccharomyces cerevisiae* were engineered to express this protein under the control of the TEF2 promoter. This fusion protein has the following sequence elements fused in frame from N- to C-terminus, represented by SEQ ID NO:52: (1) an N-terminal peptide to impart resistance to proteasomal degradation and stabilize or enhance expression (SEQ ID NO:56, or positions 1 to 89 of SEQ ID NO:52); (2) a two amino acid spacer/linker (Thr-Ser) to facilitate cloning and manipulation of the sequences (positions 90 to 91 of SEQ ID NO:52); (3) positions 2-944 of Ad-36 hexon (positions 2-944 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 92-1034 of SEQ ID NO:52; and (3) a hexahistidine tag (positions 1035-1040 of SEQ ID NO:52). This construct contains demonstrated or

putative MHC Class I epitopes (e.g., positions 204-214 of SEQ ID NO:52; positions 404-412 of SEQ ID NO:52; positions 795-803 of SEQ ID NO:52; positions 928-936 of SEQ ID NO:52; or positions 994-1000 of SEQ ID NO:52), and demonstrated or putative MHC Class II epitopes (e.g., positions 100-110 of SEQ ID NO:52; positions 116-126 of SEQ ID NO:52; 406-420 of SEQ ID NO:52; positions 458-468 of SEQ ID NO:52; positions 792-803 of SEQ ID NO:52; or positions 947-957 of SEQ ID NO:52). The amino acid segments used in this fusion protein can be modified by the use of additional amino acids flanking either end of any domain. The nucleic acid sequence encoding the fusion protein of SEQ ID NO:44 was codon optimized for expression in yeast, and the yeast-based immunotherapeutic expressing this fusion protein was produced as described above.

The expression of this Ad-36 hexon fusion protein in yeast is shown in FIG. 2 (aFL-Hexon-F). The estimated expression level of this protein was 25,315 ng/Y.U.

Another yeast-based immunotherapeutic, denoted in FIG. 1 as "CRAG", was designed to express an Ad-36 fusion protein as a single polypeptide comprising portions of the Ad-36 CR1 α and CR1 γ proteins (the full CR1 α protein is represented by SEQ ID NO:26 and the full CR1 γ protein is represented by SEQ ID NO:29), fused at its N-terminus to a synthetic peptide represented by SEQ ID NO:58. *Saccharomyces cerevisiae* were engineered to express this protein under the control of the TEF2 promoter. This fusion protein has the following sequence elements fused in frame from N- to C-terminus, represented by SEQ ID NO:47: (1) an N-terminal peptide to impart resistance to proteasomal degradation and stabilize expression (positions 1 to 6 of SEQ ID NO:47); (2) positions 18-60 of CR1 α (positions 18-60 of SEQ ID NO:26 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 7-49 of SEQ ID NO:47; (3) positions 123-157 of Ad-36 CR1 α (positions 123-157 of SEQ ID NO:26 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 50-84 of SEQ ID NO:47; (4) positions 19-60 of Ad-36 CR1 γ (positions 19-60 of SEQ ID NO:29 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 85-126 of SEQ ID NO:47; (5) positions 83-116 of Ad-36 CR1 γ (positions 83-116 of SEQ ID NO:29 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 127-160 of SEQ ID NO:47; and (6) a hexahistidine tag (positions 161-166 of SEQ ID NO:47). The amino acid segments used in this fusion protein can be modified by the use of additional amino acids flanking either end of any domain. The nucleic acid sequence encoding the fusion protein of SEQ ID NO:43 was codon optimized for expression in yeast, and the yeast-based immunotherapeutic expressing this fusion protein was produced as described above.

The expression of this Ad-36 CR1 α -CR1 γ fusion protein is shown in FIG. 1 (CRAG). The estimated expression level of this protein was 3341 ng/Y.U.

Another yeast-based immunotherapeutic, denoted "aFL-CRAG" in FIG. 2, was designed to express an Ad-36 fusion protein as a single polypeptide comprising portions of the Ad-36 CR1 α and CR1 γ proteins (the full CR1 α protein is represented by SEQ ID NO:26 and the full CR1 γ protein is represented by SEQ ID NO:29), fused at its N-terminus to yeast alpha factor leader sequence (SEQ ID NO:56). *Saccharomyces cerevisiae* were engineered to express this protein under the control of the CUP1 promoter. This fusion protein has the following sequence elements fused in frame from N- to C-terminus, represented by SEQ ID NO:54: (1) an N-terminal peptide to impart resistance to proteasomal degradation

and stabilize or enhance expression (SEQ ID NO:56, or positions 1 to 89 of SEQ ID NO:54); 2) a two amino acid spacer/linker (Thr-Ser) to facilitate cloning and manipulation of the sequences (positions 90 to 91 of SEQ ID NO:54); (3) positions 18-60 of CR1 α (positions 18-60 of SEQ ID NO:26 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 92-134 of SEQ ID NO:54; (4) positions 123-157 of Ad-36 CR1 α (positions 123-157 of SEQ ID NO:26 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 135-169 of SEQ ID NO:54; (5) positions 19-60 of Ad-36 CR1 γ (positions 19-60 of SEQ ID NO:29 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 170-211 of SEQ ID NO:54; (6) positions 83-116 of Ad-36 CR1 γ (positions 83-116 of SEQ ID NO:29 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 212-245 of SEQ ID NO:54; and (7) a hexahistidine tag (positions 246-251 of SEQ ID NO:54). The amino acid segments used in this fusion protein can be modified by the use of additional amino acids flanking either end of any domain. The nucleic acid sequence encoding the fusion protein of SEQ ID NO:54 was codon optimized for expression in yeast, and the yeast-based immunotherapeutic expressing this fusion protein was produced as described above. The expression of this Ad-36 CR1 α -CR1 γ fusion protein is shown in FIG. 2 (aFL-CRAG). The estimated expression level of this protein was 16,154 ng/Y.U.

Additional yeast-based immunotherapeutic compositions have been designed by the inventors and are produced using the same protocols described above. For example, another yeast-based immunotherapeutic is designed to express an Ad-36 fusion protein as a single polypeptide comprising the full-length Ad-36 hexon protein (the full hexon protein is represented by SEQ ID NO:18), fused at its N-terminus to a synthetic peptide represented by SEQ ID NO:58. *Saccharomyces cerevisiae* are engineered to express this protein under the control of the TEF2 or CUP1 promoter. This fusion protein has the following sequence elements fused in frame from N- to C-terminus, represented by SEQ ID NO:44: (1) an N-terminal peptide to impart resistance to proteasomal degradation and stabilize expression (positions 1 to 6 of SEQ ID NO:44); (2) positions 2-944 of Ad-36 hexon (positions 2-944 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 7-949 of SEQ ID NO:44; and (3) a hexahistidine tag (positions 950-955 of SEQ ID NO:44). This construct contains demonstrated or putative MHC Class I epitopes (e.g., positions 119-129 of SEQ ID NO:44; positions 319-327 of SEQ ID NO:44; positions 710-718 of SEQ ID NO:44; positions 843-851 of SEQ ID NO:44; or positions 909-915 of SEQ ID NO:44), and demonstrated or putative MHC Class II epitopes (e.g., positions 15-25 of SEQ ID NO:44; positions 31-41 of SEQ ID NO:44; 321-335 of SEQ ID NO:44; positions 373-383 of SEQ ID NO:44; positions 707-718 of SEQ ID NO:44; or positions 862-872 of SEQ ID NO:44). The amino acid segments used in this fusion protein can be modified by the use of additional amino acids flanking either end of any domain; the example provided herein is exemplary. A nucleic acid sequence encoding the fusion protein of SEQ ID NO:44 is codon optimized for expression in yeast, and a yeast-based immunotherapeutic expressing this fusion protein is produced as described above.

Another yeast-based immunotherapeutic is designed to express an Ad-36 fusion protein as a single polypeptide comprising portions of the Ad-36 fiber and hexon proteins (full protein represented by SEQ ID NO:34 (fiber) and SEQ ID NO:18 (hexon)), fused at its N-terminus to a synthetic peptide

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represented by SEQ ID NO:58. *Saccharomyces cerevisiae* are engineered to express this protein under the control of the TEF2 or CUP1 promoter. This fusion protein has the following sequence elements fused in frame from N- to C-terminus, represented by SEQ ID NO:45: (1) an N-terminal peptide to impart resistance to proteasomal degradation and stabilize expression (positions 1 to 6 of SEQ ID NO:45); (2) positions 71-136 of Ad-36 fiber (positions 71-136 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 7-72 of SEQ ID NO:45; (3) positions 145-169 of Ad-36 fiber (positions 145-169 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 73-97 of SEQ ID NO:45; (4) positions 290-313 of Ad-36 fiber (positions 290-313 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 98-194 of SEQ ID NO:45; (5) positions 334-363 of Ad-36 fiber (positions 334-363 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 195-224 of SEQ ID NO:45; (6) positions 136-218 of Ad-36 hexon (positions 136-218 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 225-307 of SEQ ID NO:45; (7) positions 235-285 of Ad-36 hexon (positions 235-285 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 308-359 of SEQ ID NO:45; (8) positions 297-308 of Ad-36 hexon (positions 297-308 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 360-371 of SEQ ID NO:45; (9) positions 410-450 of Ad-36 hexon (positions 410-450 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 372-412 of SEQ ID NO:45; and (10) a hexahistidine tag (positions 413-418 of SEQ ID NO:45). The amino acid segments used in this fusion protein can be modified by the use of additional amino acids flanking either end of any domain; the example provided herein is exemplary. A nucleic acid sequence encoding the fusion protein of SEQ ID NO:45 is codon optimized for expression in yeast, and the yeast-based immunotherapeutic expressing this fusion protein is produced as described above.

Yet another yeast-based immunotherapeutic is designed to express an Ad-36 fusion protein as a single polypeptide comprising portions of the Ad-36 hexon and fiber proteins (full protein represented by SEQ ID NO:18 (hexon) and SEQ ID NO:34 (fiber)) fused at its N-terminus to a synthetic peptide represented by SEQ ID NO:58. *Saccharomyces cerevisiae* are engineered to express this protein under the control of the TEF2 or CUP1 promoter. This fusion protein has the following sequence elements fused in frame from N- to C-terminus, represented by SEQ ID NO:46: (1) an N-terminal peptide to impart resistance to proteasomal degradation and stabilize expression (positions 1 to 6 of SEQ ID NO:46); (2) positions 136-218 of Ad-36 hexon (positions 136-218 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 7-89 of SEQ ID NO:46; (3) positions 235-285 of Ad-36 hexon (positions 235-285 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 90-141 of SEQ ID NO:46; (4) positions 297-308 of Ad-36 hexon (positions 297-308 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 142-153 of SEQ ID NO:46; (5) positions 410-450 of Ad-36 hexon (positions 410-450 of SEQ ID NO:18 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 154-194 of SEQ ID NO:46; (6) positions 71-136 of Ad-36 fiber (positions

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71-136 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 195-260 of SEQ ID NO:46; (7) positions 145-169 of Ad-36 fiber (positions 145-169 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 261-285 of SEQ ID NO:46; (8) positions 290-313 of Ad-36 fiber (positions 290-313 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 286-382 of SEQ ID NO:46; (9) positions 334-363 of Ad-36 fiber (positions 334-363 of SEQ ID NO:34 or a corresponding sequence from another Ad-36 strain or isolate), corresponding to positions 383-412 of SEQ ID NO:46; and (10) a hexahistidine tag (positions 413-418 of SEQ ID NO:46). The amino acid segments used in this fusion protein can be modified by the use of additional amino acids flanking either end of any domain; the example provided herein is exemplary. A nucleic acid sequence encoding the fusion protein of SEQ ID NO:46 is codon optimized for expression in yeast, and the yeast-based immunotherapeutic expressing this fusion protein is produced as described above.

Example 2

Infection/Replication of Ad-36 in Rat Stem Cells and A549 Cells

The following example describes the ability of Ad-36 to infect primary preadipocytes and A549 cells. This experiment demonstrates that viral stock that is intended for use in vivo experiments described in the examples below is biologically active and can infect target cells of relevance in vitro. Ad-36 is a DNA virus and lacks mRNA. Transcription of Ad-36 genes into mRNA does not occur unless the virus has infected a mammalian host cell. The presence of Ad-36 mRNAs in the target cells is therefore direct evidence of viral infection and replication.

Purified Ad-36 viral stock was added to rat adipose derived stem cells (ASC) and to A549 cells (human lung carcinoma line that is a natural host cell for human adenoviruses) in culture at a multiplicity of infection (MOI) of 5. Fifteen hours post-viral addition, total RNA was isolated from the target cells and was subjected to real-time reverse transcription PCR (RT-PCR) with fluorescent SYBR green designed to specifically measure the rate of PCR amplification of E1A, E4 orf1, and Hexon mRNAs. The relative expression of these genes was determined for mock-infected or Ad-36 infected targets. The results, shown in FIG. 3 (ASC) and FIG. 4 (A549) show the E1A and Hexon genes were expressed in both cellular targets and that the E4 Orf1 was expressed specifically in A549 cells. Gene expression required the addition of Ad-36, since mock infected cells showed only background levels of signal in all reactions.

Example 3

Rat Pilot Study-Ad36 Kinetics, and Infection of Visceral Fat Tissues

The following example describes the ability of the Ad-36 stock to infect rats in vivo and evaluates: i) the optimal dose of Ad-36 giving rise to successful viral inoculation, otherwise known as 'viral take'; ii) the kinetics of the blood viremic phase of infection; iii) the ability of the virus to infect the visceral adipose tissue.

Prior to the present invention, to the inventors' knowledge, there were no kinetic or dosing experiments or fat localization

studies available that were robust enough or sufficient to establish an optimal animal model of Ad-36 infection that would be useful to evaluate prophylactic and therapeutic vaccine efficacy. Accordingly, the following experiments were designed to provide this information and to establish a relevant and useful model for studying Ad-36 infection (acute and chronic). Briefly, rats were injected intraperitoneally with PBS only or purified Ad-36 viral particles at 3 doses (10^7 , 10^8 or 10^9 plaque forming units (PFU)), according to the protocol shown in Table 2. Blood samples were taken from rats at days 0 (pre-challenge) and days 1 post challenge (20 h), and at days 2 and 4 post-challenge. Virus DNA was prepared from 100 μ l plasma using the QIAAMP® MINELUTE® Virus Kit (Qiagen), and the level of viral DNA was estimated by real time quantitative PCR (qPCR) featuring an Ad-36 hexon-DNA specific probe. Estimates of viral copy number were obtained by interpolation against a standard curve produced with purified hexon plasmid of known copy number. At two weeks post-challenge, rats were euthanized, the visceral fat was dissected and total DNA was isolated from the fat tissue using a proteinase K/isopropanol precipitation method. The DNA was subjected to nested two-round PCR featuring hexon DNA-specific PCR primers.

TABLE 2

Group	# Rats	Ad36 Dose (PFU)	Total V.P. injected	Route	Blood Draws (days post-challenge)				Fat Tissue Dissection
A	2	0	0	i.p.	d0	d1	d2	d4	d14
B	2	10^7	2.3×10^9	i.p.	d0	d1	d2	d4	d14
C	2	10^8	2.3×10^{10}	i.p.	d0	d1	d2	d4	d14
D	2	10^9	2.3×10^{11}	i.p.	d0	d1	d2	d4	d14

Results showing the virus particle (V.P.) copies per ml blood at each level of viral infection are provided in FIG. 5 (Group A; mock control); FIG. 6 (Group B; 10^7 PFU Ad-36); FIG. 7 (Group C; 10^8 PFU Ad-36); and FIG. 8 (Group D; 10^9 PFU Ad-36). FIG. 9 shows the results of PCR to detect Ad-36 hexon in visceral fat. Taken together, the results of these experiments demonstrate that: 1) the level of Ad-36 virus in the blood as determined by hexon qPCR is maximal at the 10^9 PFU dose, and at 20 h post challenge; and 2) the Ad-36 virus is present in the visceral adipose tissue of all rats by 2 weeks post challenge at the 10^8 and 10^9 PFU doses, whereas at the 10^7 PFU dose, virus was robustly detectable in the adipose tissue of only one of the two rats. These data show that the purified Ad-36 stock that was shown to infect primary preadipocytes in culture in Example 2 are also infective in vivo, and confirm published reports (e.g., Pasarica et al, 2008) that Ad-36 infects visceral adipose tissues. Since the maximal levels of viremia occurred with injection of 10^9 PFU (see FIG. 8), this dose was selected for challenge of rats in the yeast-based immunotherapy vaccination experiments described in the following examples. Accordingly, these data were used to establish an optimized rat model system of Ad-36 infection for the testing of prophylactic and therapeutic vaccines (immunotherapy).

Example 4

Effect of Prophylactic Administration of Ad-36 Tarmogens in the Rat Model of Ad-36 Infection

The following example describes the use of yeast-based adenovirus-36 (Ad-36) immunotherapeutics in rat prophylactic model of adenovirus-related obesity.

A rat model has been studied in the literature (Dhurandhar et al, Obesity 11:1905, 2006) in which Ad36-infected rats attained significantly greater body weight and fat pad weight by 30 weeks post-inoculation than mock infected control rats. Epididymal-inguinal, retroperitoneal, and visceral fat pad weights of the infected group were greater than PBS control rats by 60%, 46%, and 86%, respectively ($p < 0.00001$). The present inventors have improved this rat model for the purposes of evaluating prophylactic and therapeutic vaccines, as described above in Example 3.

The following experiment describes a study to determine if prophylactic administration of the yeast-based immunotherapeutic compositions described in Example 1 prevent or reduce the extent of or rate of Ad-36-induced weight gain.

Cohorts of rats ($n=18$ /group) were immunized subcutaneously (s.c.) with yeast-based Ad-36 immunotherapeutic compositions (vaccines), administered at four different sites with 20 million yeast cells (2 Y.U.) in 0.1 ml per site. In these experiments, two different yeast-based immunotherapeutic compositions were used. "Ad-aFL-CRAG" is the yeast-based immunotherapeutic described in Example 1 above that expresses an Ad-36 fusion protein comprising Ad-36 CR1 α and CR1 γ antigens, these antigens having an amino acid sequence of SEQ ID NO:55, which are linked at the N-terminus to an alpha factor leader sequence, to form a complete fusion protein having the amino acid sequence of SEQ ID NO:54. "Ad-aFL-HEX-Full" is the yeast-based immunotherapeutic described in Example 1 above that expresses an Ad-36 fusion protein comprising a near full-length hexon antigen, the antigen having an amino acid sequence of SEQ ID NO:53, which is linked at its N-terminus to an alpha factor leader sequence, to form a complete fusion protein having the amino acid sequence of SEQ ID NO:52. Dosing was once per week for 3 weeks and then, after a two week rest, rats were challenged intraperitoneally with Ad-36 (10^9 PFU), which was established in Example 3 to be the optimal viral dose for evaluating Ad-36 infection. Immunization was then conducted once per month for up to 30 weeks post-challenge. The experimental cohorts are shown in Table 3. Additional control groups include a group of rats receiving PBS only (naïve or "PBS"), and a group of rats immunized with control yeast compositions ("empty vector" yeast or "YVEC", which are yeast transfected with a vector that does not contain an antigen insert; i.e., these yeast do not express an Ad-36 antigen(s)).

TABLE 3

Group	Pre-challenge Immunization	Challenge	Post-challenge Immunization
A	PBS	PBS	PBS
B	PBS	Ad-36	PBS
C	YVEC	Ad-36	YVEC
D	Yeast-Ad-aFL-CRAG	Ad-36	Ad-aFL-CRAG
E	Yeast-Ad-aFL-HEX-Full	Ad-36	Ad-aFL-HEX-Full

Animals were weighed pre-immunization, pre-viral challenge and then biweekly for approximately 30 weeks following inoculation with virus. Food and water consumption were monitored throughout the study. Blood was collected at baseline, before viral challenge, and monthly following viral challenge to monitor for Ad-36 DNA, cholesterol, triglyceride levels, corticosterone, neutralizing antibodies to Ad-36, and other parameters (see Example 5). Glucose tolerance testing is performed at selected intervals and urine glucose levels are

also measured. Blood (500 μ l per timepoint) was obtained under isoflurane anesthesia from the tail vein. At the end of the study, animals are euthanized and adipose tissue is harvested to measure viral levels by polymerase chain reaction (PCR). PCR may also be performed on biopsies obtained during the course of the study.

This experiment was performed in outbred Wistar rats. If, as expected, weight gain is prevented or reduced (or the rate of weight gain is reduced) in rats immunized with yeast-based Ad-36 immunotherapy as compared to control rats, inbred Wistar Furth rats will be evaluated according to the same or similar protocol, as this rat is expected to be more amenable to evaluation of T cell immunity. Additional experiments can also be conducted to determine the effect of diet or other factors in conjunction with immunotherapy (e.g., by administering a high fat diet versus a normal diet).

Immunization with a yeast-based Ad-36 immunotherapy composition is deemed active in this study if it causes, as compared with empty vector yeast or PBS controls, notable trends towards normalization of or beneficial outcome (more healthy, less characteristic of obesity or being or becoming overweight) in any one or more of the following parameters for Ad-36 infected rats: i) body weight or rate of body weight gain; ii) percent body fat or body mass index; iii) frequency or titer of neutralizing antibodies; iv) cholesterol levels; v) serum triglycerides vi) serum corticosterone; vii) blood and/or urine glucose levels; viii) glucose tolerance; ix) blood Ad-36 viral titer. Certain of these parameters have already been observed as positive indicators of the effectiveness of Ad-36-targeted yeast-based immunotherapy in immunized rats (see following discussion) at 18 weeks post-challenge, and are believed to show that yeast-based immunotherapy targeting Ad-36 is effective for reducing the rate of weight gain in an antigen-specific manner. It is expected that by the end of the study at 30 weeks when the Ad-36 induced phenotype fully emerges, the results will demonstrate that immunization with a yeast-based Ad-36 immunotherapy composition is effective for reducing and/or preventing weight gain, reducing rate of weight gain, and/or reducing or preventing adiposity in rats infected with Ad-36 in an antigen-specific or Ad-36-specific manner, and this may be accompanied by changes in the biochemical parameters mentioned, given their known association with the obesity phenotype.

As discussed above, the present study is currently at week 18 post-viral challenge. Virus-induced weight gain in control rats is not anticipated to be measurable at this early time-point based on work by Dhurandhar (Dhurandhar et al 2006). Consistent with this expectation, the weight gain data through week 18 show that Ad-36 challenge has not yet caused weight gain above PBS injected control rats. However, the aFL-CRAG Tarmogen immunization group already has a lower overall weight gain than rats in the other groups, as shown in FIGS. 10, 11 and 12. Specifically, FIG. 10 is a scatter plot showing individual rats in each of the immunization groups, and revealing a clear trend in the yeast-based immunotherapy groups, and particularly in the rats immunized with a yeast-based immunotherapeutic expressing Ad-36 CR1 α and CR1 γ , toward a lower rate of weight gain as compared to rats immunized with PBS only (PBS) or with the "empty vector" yeast control (YVEC). FIG. 11 shows the median weight gain for each group of animals over time. Again, the reduced rate of weight gain as compared to controls in the rats immunized with yeast-based immunotherapeutic expressing Ad-36 CR1 α and CR1 γ is clear. FIG. 12 illustrates two individual time points (4 weeks post-viral challenge and 12 weeks post-viral challenge) and again, the reduced rate of weight gain in rats immunized with yeast-Ad-36 immunotherapy as com-

pared to the PBS control is evident (p values are relative to the PBS control). Error bars in FIG. 12 are generated based on comparison to the PBS-immunized, virus-challenged control group and statistical significance is measured also as compared to this group.

Taken together, these data demonstrate an Ad-36-specific, and particularly, an Ad-36 CR1 α -CR1 γ -antigen specific effect, of the yeast-based immunotherapeutic on body weight gain, and one that has emerged before an Ad-36 emergent obesity phenotype is even apparent. A plot of the body weight at weeks 4 and 12 shows that this the weight gain of aFL-CRAG immunized rats is statistically significantly lower than the weight gain of YVEC (control yeast) or Naive rats (PBS) at these time-points (FIG. 12). The rats immunized with the yeast expressing a hexon-based fusion protein show a trend toward a similar phenotype, although at this time point, the difference from controls is not as substantial as for the yeast expressing the CR1 α -CR1 γ -antigen. Therefore, yeast-based immunotherapy targeting Ad-36 reduces the rate of weight gain in an animal model of chronic Ad-36 infection, and is expected to show reduced weight gain and additional benefits, as compared to the controls, with respect to the other parameters discussed above by 30 weeks post-challenge.

Example 5

Viral Kinetics in the Prophylactic Ad-36 Yeast-Based Immunotherapy Study (Rat)

The following experiment demonstrates the use of the method described in Example 4 to test Ad-36 viral kinetics in the bloodstream after Ad-36 viral challenge.

Briefly, blood genomic DNA was extracted from 100 μ l of rat blood using Qiagen's QIAamp Kit. Ad-36 DNA was detected by quantitative polymerase chain reaction (qPCR), featuring a unique Hexon-gene specific probe designed by the inventors. The results, illustrated in FIG. 13, show that Ad-36 DNA is present at 10^6 to 10^9 copies per mL for up to 9 weeks post-challenge, and was cleared from the blood completely by 13 weeks post-challenge. Interestingly, the inter-rat variability of viral DNA load decreases over time, reaching a minimum just before clearance. Without being bound by theory, the inventors believe that these data could reflect the natural immune response to the virus, the yeast-based immunotherapy-induced immune response to the virus, or some combination of these effects.

Example 6

Rat Therapeutic Experiment

The following example describes the use of yeast-based Ad-36 immunotherapeutics in a rat therapeutic model of adenovirus-related obesity.

In the following experiment, yeast-based Ad-36 immunotherapeutic compositions (vaccines) were evaluated to determine whether immunization against this virus using yeast-based immunotherapy can reverse obesity or at least reduce weight gain or the rate of weight gain and adiposity in rats when immunization with yeast-based Ad-36 compositions is initiated after Ad-36 infection and subsequent weight gain.

Rats were infected with Ad-36 (approximately 1×10^9 PFU in 1 ml) by intraperitoneal administration, as described in the prophylactic study in Example 4. After an Ad-36 emergent obesity phenotype has been established, groups of rats are immunized subcutaneously (s.c.) with one of the two yeast-based Ad-36 immunotherapeutic compositions (vaccines)

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described in Example 4 above and in Table 4 below, administered at four different sites, with 20 million cells (2.0 Y.U.) s.c. in 0.1 ml per site. Vaccinations are performed once per week for 2 weeks after challenge, and then monthly for as long as 30 weeks. Additional control groups include a group of rats immunized with control yeast compositions ("empty vector" yeast, or YVEC, that do not express the Ad-36 antigen(s)), and a group of rats receiving PBS only (naïve or PBS). In the present example the control group (B) is PBS.

TABLE 4

Group	challenge	Post-challenge Immunization
B	Ad-36	PBS
F	Ad-36	Ad-aFL-CRAG
H	Ad-36	Ad-aFL-HEX-Full

Animals are weighed pre-viral infection and then up to biweekly for the up to 30 weeks duration of the study. In addition, food and water consumption are monitored. Blood is collected pre-viral infection and biweekly to monitor for serum viral load, cholesterol, triglyceride levels, corticosterone, neutralizing antibodies, and the other biochemical parameters as described in Example 5. Glucose tolerance testing is performed and glucose levels are measured in the urine. Blood (500 µl per timepoint) is obtained under isoflurane anaesthesia from the tail vein.

At the end of the study, animals are euthanized and adipose tissue is harvested to measure viral levels by polymerase chain reaction (PCR). PCR may also be performed on biopsies obtained during the course of the study.

This experiment was performed in outbred Wistar rats. If, as expected, additional weight gain is prevented or reduced in rats immunized with yeast-based Ad-36 immunotherapy as compared to control rats, inbred Wistar Furth rats will be evaluated according to the same or similar protocol, as these inbred rats are expected to be more amenable to evaluation of T cell immunity. Additional experiments may also determine the effect of diet or other factors in conjunction with immunotherapy (e.g., by administering a high fat diet versus a normal diet).

Immunization with a yeast-based Ad-36 immunotherapy composition is deemed active if it causes, as compared with empty vector yeast or PBS controls, notable trends towards normalization of any of the following parameters for Ad-36 infected rats: i) body weight or a reduced rate of body weight gain; ii) percent body fat or body mass index; iii) frequency or titer of neutralizing antibodies; iv) cholesterol levels; v) serum corticosterone; vi) serum triglycerides; vii) blood and/or urine glucose levels; viii) glucose tolerance; ix) blood Ad-36 viral titer. In summary, it is expected that immunization with a yeast-based Ad-36 immunotherapy composition will be effective for reducing or preventing weight gain and adiposity in rats and this may be accompanied by changes in the biochemical parameters mentioned, given their known association with the obesity phenotype.

Example 7

Effect of Yeast Vector on Rat Appetite and Body Weight Gain

The following example describes an experiment designed to determine if immunization of rats with yeast-based immunotherapeutic compositions of the invention affects the rate of weight gain of naive uninfected (not infected with Ad-36)

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rats. This experiment was designed to identify whether there is a yeast vector-based effect of Tarmogen vaccination on appetite or body weight gain that is independent of Ad-36 exposure. Such effects on appetite or body weight, if observed, would not be considered to be antigen-specific, since there is no viral antigen in the host, and would be important to determine prior to interpreting the effect of Ad-36 Tarmogen immunization on Ad-36-induced weight gain.

Rats were immunized with one of the yeast-based immunotherapy compositions described in Example 1 (Ad-Fib, the fusion protein of which is represented by SEQ ID NO:42) once per week, on weeks 1, 2, 7, 9, and 11. Vaccination was at 4 s.c sites with 2 Y.U. per site. The animals were weighed pre-immunization and biweekly following vaccination. The diet consumption and body weight of the rats was monitored during this period. The results, shown in FIG. 14, show that there was no difference in food consumption between the yeast-immunized group and control group. Also, Ad-Fiber yeast vaccination did not change the rate of body weight gain as compared to naive control rats, as shown in FIG. 15. These data demonstrate that yeast based immunotherapy vaccinations per se (in the absence of the target antigen) do not alter the appetite or body weight gain of rats. These results are consistent with the observation that the effects of Ad-36 yeast-based immunotherapy on body weight, when observed in the Ad-36 challenge experiments described above, are not believed to be attributable to a generalized effect of the yeast or yeast vector on rat appetite or metabolism.

Example 8

Organ Distribution of Ad-36 after Intraperitoneal Inoculation

The following experiment demonstrates the Ad36 distribution in major organs and tissues after the virus infection.

This experiment is of relevance to the specificity/tropism of the virus and to the best of the inventors' knowledge, such analyses have not been conducted in any study this late after viral challenge. Therefore, the following experiments were designed to confirm that Ad-36 resides in fat compartments after the virus is no longer detectable in the blood, and to further indicate tissues or organs where yeast-based immunotherapy may be active. In one published study (Pasaricia et al, 2008), conducted at 4 days post challenge, Ad-36 was found in nearly all tissues tested including the central nervous system (CNS), heart, lung, liver, spleen, kidney, visceral fat, and other organs. In the present study, the organ/body-wide distribution of Ad-36 was evaluated at 15 weeks virus post-challenge in a non-immunized rat. Briefly, major organs and tissues (include blood and peripheral blood mononuclear cells (PBMC)) were removed and isolated. Organ and tissue genomic DNA was extracted from all samples using the QIAamp Kit, and Ad-36 DNA was detected with a very sensitive nested polymerase chain reaction (PCR) assay. The results, shown in FIG. 16, indicated that 15 weeks after virus inoculation, Ad-36 DNA is detectable in the epididymal, retroperitoneal, omental visceral adipose tissues, and also in the spleen and kidney. However, Ad36 DNA was absent from heart, liver, lung, brain, and subcutaneous fat, as well as the other organs/tissues tested. These results, taken together with the prior results of Pasarica et al., show that Ad-36, although widely distributed in most major organs early after challenge,

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becomes more localized to fat compartments, as well as kidney and spleen, by 15 weeks post viral challenge.

Example 9

Mouse Model-Propylactic

The following example describes the use of yeast-based adenovirus-36 (Ad-36) immunotherapeutics in an animal model of adenovirus-related obesity.

A mouse model has been described in the literature whereby infection of animals with human Ad-36 has caused weight gain and increase in adiposity (Dhurandhar et al. *Int. J. Obesity* 24:989, 2000). In those studies, a statistically significant increase in body fat weight ($p < 0.02$) was elicited in Ad36-infected mice compared to the control group. Additionally, 60% of Ad-36 injected mice vs. 22% of controls were considered obese when obesity was defined as >85 th percentile of the control group.

In the following experiment, yeast-based Ad-36 immunotherapeutic compositions (vaccines) are evaluated to determine whether immunization against this virus using yeast-based immunotherapy can prevent obesity or at least reduce weight gain and adiposity associated with Ad-36 infection.

Groups of mice are immunized subcutaneously (s.c.) with a yeast-based Ad-36 immunotherapeutic composition (vaccine) administered at two to four different sites (1 to 20 million cells (or 0.1-2.0 Y.U.) s.c. in 0.1 ml per site), between three and six times at weekly intervals. After the final administration, mice are challenged with Ad-36 (approximately 2×10^7 PFU in 0.1-0.2 ml) by intraperitoneal administration. Experimental groups of mice (10-20 mice per group) are immunized with a yeast-based Ad-36 immunotherapeutic composition, e.g., one of the yeast-based immunotherapy compositions described in Example 1. Additional control groups include a group of mice immunized with control yeast compositions ("empty vector" yeast that do not express the Ad-36 antigen(s)), and a group of mice receiving PBS only (naïve).

Animals are weighed pre-treatment, pre-viral challenge and then up to twice weekly for approximately 22 weeks following inoculation with virus. In addition, food and water consumption are monitored. Blood is collected at baseline, pre-viral challenge and biweekly following challenge to monitor for cholesterol, triglyceride levels and for neutralizing antibodies to Ad36 in the serum. Glucose tolerance testing is performed and glucose levels are measured in the urine. Blood (200 μ l per timepoint) is obtained under isofluroane anaesthesia from the retro-orbital plexus. At the end of the study, animals are euthanized and adipose tissue is harvested to measure viral levels by polymerase chain reaction (PCR). PCR may also be performed on biopsies obtained during the course of the study.

The experiment is initially performed in outbred mice (e.g., ICR or CD-1® mice). If, as expected, weight gain is prevented or reduced in mice immunized with yeast-based Ad-36 immunotherapy as compared to control mice, inbred strain(s) are further evaluated according to the same or similar protocol (e.g., C57BL/6, BALB/c or C3H), as these mice are expected to be more amenable to evaluation of T cell immunity. Additional experiments may also determine the effect of diet or other factors in conjunction with immunotherapy (e.g., by administering a high fat diet versus a normal diet).

Immunization with a yeast-based Ad-36 immunotherapy composition is effective if immunization results in a statistically significant difference in body weight or body weight gain between yeast-Ad-36 immunized mice and control mice

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(empty vector yeast or PBS-immunized), and/or at least a two-fold difference in neutralizing antibody levels, and/or a greater than 5% reduction in percent body fat, cholesterol, triglycerides, reduction in glucose in the urine or reduced glucose levels by glucose tolerance test and/or reduction in Ad-36 viral titers, between the experimental and either control group (empty vector yeast or PBS-immunized). It is expected that immunization with a yeast-based Ad-36 immunotherapy composition will be effective for reducing or preventing weight gain and adiposity in mice.

Example 10

Mouse Model-Therapeutic

The following example describes the use of yeast-based Ad-36 immunotherapeutics in an animal model of adenovirus-related obesity.

In the following experiment, yeast-based Ad-36 immunotherapeutic compositions (vaccines) are evaluated to determine whether immunization against this virus using yeast-based immunotherapy can reverse obesity or at least reduce weight gain and adiposity in mice when immunization with yeast based Ad-36 compositions is initiated after Ad-36 infection and subsequent weight gain.

Mice are infected with Ad-36 (approximately 2×10^7 PFU in 0.1-0.2 ml) by intraperitoneal administration. Once weight gain has been established, groups of mice will be immunized subcutaneously (s.c.) with a yeast-based Ad-36 immunotherapeutic composition (vaccine) administered at two to four different sites (1 to 20 million cells (0.1 to 2.0 Y.U.) s.c. in 0.1 ml per site), between three and six times at weekly intervals. Additional control groups include a group of mice immunized with control yeast compositions ("empty vector" yeast that do not express the Ad-36 antigen(s)), and a group of mice receiving PBS only (naïve).

Animals are weighed pre-viral infection and then up to twice weekly for the duration of the study. In addition, food and water consumption are monitored. Blood is collected pre-viral infection and biweekly to monitor for cholesterol, triglyceride levels and for neutralizing antibodies to Ad36 in the serum. Glucose tolerance testing is performed and glucose levels are measured in the urine. Blood (200 μ l per timepoint) is obtained under isofluroane anaesthesia from the retro-orbital plexus.

At the end of the study, animals are euthanized and adipose tissue is harvested to measure viral levels by polymerase chain reaction (PCR). PCR may also be performed on biopsies obtained during the course of the study.

The experiment is initially performed in outbred mice (e.g., ICR or CD-1® mice). If, as expected, additional weight gain is prevented or reduced in mice immunized with yeast-based Ad-36 immunotherapy as compared to control mice, inbred strain(s) are further evaluated according to the same or similar protocol (e.g., C57BL/6, BALB/c or C3H), as these mice are expected to be more amenable to evaluation of T cell immunity. Additional experiments may also determine the effect of diet or other factors in conjunction with immunotherapy (e.g., by administering a high fat diet versus a normal diet).

Immunization with a yeast-based Ad-36 immunotherapy composition is effective if immunization results in a statistically significant difference in body weight or body weight gain between yeast-Ad-36 immunized mice and control mice (empty vector yeast or PBS-immunized), and/or at least a two-fold difference in neutralizing antibody levels, and/or a greater than 5% reduction in percent body fat, cholesterol, triglycerides in glucose in the urine or reduced glucose levels

by glucose tolerance test and/or reduction in Ad-36 viral titers between the experimental and either control group (empty vector yeast or PBS-immunized). It is expected that immunization with a yeast-based Ad-36 immunotherapy composition will be effective for reducing or preventing additional weight gain and adiposity in mice.

Example 11

Treatment of Ad-36 Infection in Humans

The following example describes a clinical trial for the treatment of Ad-36 infection in human adult subjects.

A randomized phase 1 clinical trial in adult patients and/or in obese pediatric patients testing positive for adenovirus-36 infection and having a BMI of at least 25 (or pediatric patients with analogous/equivalent BMI) will be conducted. Additional groups or trials include non-obese and/or non-overweight adults and/or pediatric patients testing positive for adenovirus infection. Subjects will be randomized into two arms. Arm 1 patients will receive at least 12 weeks of yeast-based Ad-36 immunotherapy (any composition as described

in Example 1) and will follow a prescribed diet and exercise regimen. Arm 2 patients will receive a placebo (PBS control injection or empty yeast) and will follow the same prescribed diet and exercise program. One primary endpoint is reduction in Ad-36 viral titer. Another endpoint is immune seroconversion determined by measurement of the presence of Ad-36 antibodies. Another endpoint is Ad-36-specific cellular immune responses (which may include T cell proliferation, induction of CD4⁺ Th1 and/or Th17 cells, induction of CD8⁺ T cells as measure by CTL assay or cytokine assay, and/or modulation in regulatory T cell (Treg) numbers or function). Additional secondary endpoints include a reduction in BMI, as well as relative weight loss and absolute weight loss during treatment and during longitudinal follow-up after completion of therapy.

While various embodiments of the present invention have been described in detail, it is apparent that modifications and adaptations of those embodiments will occur to those skilled in the art. It is to be expressly understood, however, that such modifications and adaptations are within the scope of the present invention, as set forth in the following exemplary claims.

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<210> SEQ ID NO 2
<211> LENGTH: 253
<212> TYPE: PRT
<213> ORGANISM: Adenovirus type 36

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<400> SEQUENCE: 2

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Met Arg His Leu Arg Leu Leu Pro Ser Thr Val Pro Gly Asp Leu Ala
1           5           10          15
Val Ile Met Leu Glu Asp Phe Val Asn Thr Val Leu Glu Asp Glu Leu
20          25          30
His Pro Glu Pro Phe Glu Leu Gly Pro Thr Leu Gln Asp Leu Tyr Asp
35          40          45
Leu Glu Val Asp Ala His Asp Asp Asp Pro Asn Glu Glu Ala Val Asn
50          55          60
Leu Ile Phe Pro Glu Ser Met Ile Leu Gln Ala Asp Ile Ala Ser Glu
65          70          75          80
Ala Ile Val Thr Pro Leu His Thr Pro Thr Leu Pro Pro Ile Pro Glu
85          90          95
Leu Glu Glu Asp Glu Glu Ile Asp Leu Arg Cys Tyr Glu Glu Gly Phe
100         105         110
Pro Pro Ser Asp Ser Glu Asp Glu Gln Gly Glu Gln Gln Met Ala Leu
115         120         125
Ile Ser Asp Leu Ala Cys Val Ile Val Glu Glu Gln Val Val Ile Glu
130         135         140
Lys Ser Thr Glu Pro Val Gln Gly Cys Arg Asn Cys Gln Tyr His Arg
145         150         155         160
Asp Lys Ser Gly Asp Pro Asn Ala Ser Cys Ala Leu Cys Tyr Met Lys
165         170         175
Ser Thr Phe Ser Phe Ile Tyr Ser Pro Val Ser Glu Asp Glu Ser Ser
180         185         190
Pro Ser Glu Glu Asp His Pro Ser Pro Pro Glu Leu Ser Gly Glu Thr
195         200         205
Pro Leu Gln Val His Arg Pro Thr Pro Val Arg Ala Ser Gly Glu Arg
210         215         220
Arg Ala Ala Val Glu Lys Ile Glu Asp Leu Leu His Asp Met Gly Gly
225         230         235         240
Asp Glu Pro Leu Asp Leu Ser Leu Lys Arg Pro Arg Asn
245         250

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<210> SEQ ID NO 3
<211> LENGTH: 191
<212> TYPE: PRT
<213> ORGANISM: Adenovirus type 36

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<400> SEQUENCE: 3

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Met Arg His Leu Arg Leu Leu Pro Ser Thr Val Pro Gly Asp Leu Ala
1           5           10          15
Val Ile Met Leu Glu Asp Phe Val Asn Thr Val Leu Glu Asp Glu Leu

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20	25	30
His Pro Glu Pro Phe Glu Leu Gly Pro Thr Leu Gln Asp Leu Tyr Asp		
35	40	45
Leu Glu Val Asp Ala His Asp Asp Asp Pro Asn Glu Glu Ala Val Asn		
50	55	60
Leu Ile Phe Pro Glu Ser Met Ile Leu Gln Ala Asp Ile Ala Ser Glu		
65	70	75
Ala Ile Val Thr Pro Leu His Thr Pro Thr Leu Pro Pro Ile Pro Glu		
85	90	95
Leu Glu Glu Asp Glu Glu Ile Asp Leu Arg Cys Tyr Glu Glu Gly Phe		
100	105	110
Pro Pro Ser Asp Ser Glu Asp Glu Gln Gly Pro Val Ser Glu Asp Glu		
115	120	125
Ser Ser Pro Ser Glu Glu Asp His Pro Ser Pro Pro Glu Leu Ser Gly		
130	135	140
Glu Thr Pro Leu Gln Val His Arg Pro Thr Pro Val Arg Ala Ser Gly		
145	150	155
Glu Arg Arg Ala Ala Val Glu Lys Ile Glu Asp Leu Leu His Asp Met		
165	170	175
Gly Gly Asp Glu Pro Leu Asp Leu Ser Leu Lys Arg Pro Arg Asn		
180	185	190

<210> SEQ ID NO 4

<211> LENGTH: 182

<212> TYPE: PRT

<213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 4

Met Asp Val Trp Thr Ile Leu Ala Asp Phe Ser Lys Thr Arg Arg Leu		
1	5	10
Val Glu Asp Ser Ser Asp Gly Cys Ser Gly Phe Trp Arg His Trp Phe		
20	25	30
Gly Thr Pro Leu Ser Arg Leu Val Tyr Thr Val Lys Lys Asp Tyr Lys		
35	40	45
Glu Glu Phe Glu Asn Leu Phe Ala Asp Cys Ser Gly Leu Leu Asp Ser		
50	55	60
Leu Asn Leu Gly His Gln Ser Leu Phe Gln Glu Arg Val Leu His Ser		
65	70	75
Leu Asp Phe Ser Ser Pro Gly Arg Thr Thr Ala Gly Val Ala Phe Val		
85	90	95
Val Phe Leu Val Asp Lys Trp Ser Gln Asp Thr Gln Leu Ser Arg Gly		
100	105	110
Tyr Ile Leu Asp Phe Ala Ala Met His Leu Trp Arg Ala Trp Ile Arg		
115	120	125
Gln Arg Gly Gln Arg Ile Leu Asn Tyr Trp Leu Leu Gln Pro Ala Ala		
130	135	140
Pro Gly Leu Leu Arg Leu His Arg Gln Thr Ser Met Leu Glu Glu Glu		
145	150	155
Met Arg Gln Ala Met Asp Glu Asn Pro Arg Ser Gly Leu Asp Pro Pro		
165	170	175
Ser Glu Glu Glu Leu Asp		
180		

<210> SEQ ID NO 5

<211> LENGTH: 495

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<212> TYPE: PRT

<213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 5

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Met Glu Pro Gly His Pro Thr Glu Gln Gly Leu His Pro Gly Leu Arg
1          5          10          15

Ser His Ala Pro Val Glu Gly Leu Asp Gln Ala Ala Gly Thr Glu Asn
          20          25          30

Leu Glu Leu Leu Ala Ser Thr Ala Ser Ser Ser Gly Ser Ser Ser Ser
          35          40          45

Thr Gln Thr Asn Ile His Val Gly Gly Arg Asn Glu Ala Gly His Gly
50          55          60

Arg Glu Pro Glu Glu Arg Pro Gly Pro Ser Val Gly Arg Gly Ala Gly
65          70          75          80

Leu Asn Gln Val Ser Ser Leu Tyr Pro Glu Leu Ser Lys Val Leu Thr
          85          90          95

Ser Met Ala Arg Gly Val Lys Arg Glu Arg Ser Asp Gly Gly Asn Thr
          100          105          110

Gly Met Met Thr Glu Leu Thr Ala Ser Leu Met Asn Arg Lys Arg Pro
          115          120          125

Glu Arg Leu Thr Trp Tyr Glu Leu Gln Gln Glu Cys Arg Asp Glu Ile
130          135          140

Gly Leu Met Gln Asp Lys Tyr Gly Leu Glu Gln Ile Lys Thr His Trp
145          150          155          160

Leu Asn Pro Asp Glu Asp Trp Glu Glu Ala Ile Lys Lys Tyr Ala Lys
          165          170          175

Ile Ala Leu Arg Pro Asp Cys Lys Tyr Ile Val Thr Lys Thr Val Asn
          180          185          190

Ile Arg His Ala Cys Tyr Ile Ser Gly Asn Gly Ala Glu Val Val Ile
          195          200          205

Asp Thr Leu Asp Lys Ala Ala Phe Arg Cys Cys Met Met Gly Met Arg
210          215          220

Ala Gly Val Met Asn Met Asn Ser Met Ile Phe Met Asn Ile Lys Phe
225          230          235          240

Asn Gly Glu Lys Phe Asn Gly Val Leu Phe Met Ala Asn Ser His Met
          245          250          255

Thr Leu His Gly Cys Ser Phe Phe Gly Phe Asn Asn Met Cys Ala Glu
          260          265          270

Val Trp Gly Ala Ala Lys Ile Arg Gly Cys Lys Phe Tyr Gly Cys Trp
          275          280          285

Met Gly Val Val Gly Arg Pro Lys Ser Glu Met Ser Val Lys Gln Cys
290          295          300

Val Phe Glu Lys Cys Tyr Leu Gly Val Ser Thr Glu Gly Asn Ala Arg
305          310          315          320

Val Arg His Cys Ser Ser Met Glu Thr Gly Cys Phe Cys Leu Val Lys
          325          330          335

Gly Thr Ala Ser Leu Lys His Asn Met Val Lys Gly Cys Thr Asp Glu
          340          345          350

Arg Met Tyr Asn Met Leu Thr Cys Asp Ser Gly Val Cys His Ile Leu
          355          360          365

Lys Asn Ile His Val Thr Ser His Pro Arg Lys Lys Trp Pro Val Phe
          370          375          380

Glu Asn Asn Leu Leu Ile Lys Cys His Met His Leu Gly Ala Arg Arg
385          390          395          400

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Gly Thr Phe Gln Pro Tyr Gln Cys Asn Phe Ser Gln Thr Lys Leu Leu
405 410 415

Leu Glu Asn Asp Ala Phe Ser Arg Val Asn Leu Asn Gly Ile Phe Asp
420 425 430

Met Asp Val Ser Val Tyr Lys Ile Leu Arg Tyr Asp Glu Thr Lys Ser
435 440 445

Arg Val Arg Ala Cys Glu Cys Gly Gly Arg His Thr Arg Met Gln Pro
450 455 460

Val Ala Leu Asp Val Thr Glu Glu Leu Arg Pro Asp His Leu Val Met
465 470 475 480

Ala Cys Thr Gly Thr Glu Phe Ser Ser Ser Gly Glu Asp Thr Asp
485 490 495

<210> SEQ ID NO 6
<211> LENGTH: 134
<212> TYPE: PRT
<213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 6

Met Asn Gly Thr Gly Gly Ala Phe Glu Gly Gly Leu Phe Ser Pro Tyr
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Leu Thr Thr Arg Leu Pro Gly Trp Ala Gly Val Arg Gln Asn Val Met
20 25 30

Gly Ser Thr Val Asp Gly Arg Pro Val Leu Pro Ala Asn Ser Ser Thr
35 40 45

Met Thr Tyr Ala Thr Val Gly Ser Ser Ser Leu Asp Ser Thr Ala Ala
50 55 60

Ala Ala Ala Ala Ala Ala Ala Met Thr Ala Thr Arg Leu Ala Ser Ser
65 70 75 80

Tyr Met Pro Ser Ser Ser Ser Ser Pro Ser Val Pro Ser Ser Ile Ile
85 90 95

Ala Glu Glu Lys Leu Leu Ala Leu Leu Ala Glu Leu Glu Ala Leu Ser
100 105 110

Arg Gln Leu Ala Ala Leu Thr Gln Gln Val Ser Glu Leu Arg Glu Gln
115 120 125

Gln Gln Gln Gln Asn Lys
130

<210> SEQ ID NO 7
<211> LENGTH: 448
<212> TYPE: PRT
<213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 7

Met Glu Thr Arg Gly Arg Arg Pro Cys Pro Phe Gln His Gln Gln Asp
1 5 10 15

Glu Ser Gln Ala His Pro Cys Lys Arg Pro Ala Arg Gly Pro Pro Leu
20 25 30

His Arg Asp Gly Asp His Thr His Ala Asp Pro Glu Thr Leu Glu Gly
35 40 45

His Asp Ala Gly Arg Ala Gly Arg Pro Ser Ser Arg Ala Leu Gln Ser
50 55 60

Gln Ser Ser Gln Pro Pro Lys Arg Gly Ser Leu Leu Asp Arg Asp Ala
65 70 75 80

Val Glu His Val Thr Glu Leu Trp Asp Arg Leu Glu Leu Leu Ser Gln
85 90 95

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Thr Leu Ala Lys Met Pro Met Ala Asp Gly Leu Lys Pro Leu Lys Asn
 100 105 110
 Phe Ala Ser Leu Gln Glu Leu Leu Ser Leu Gly Gly Asp Arg Leu Leu
 115 120 125
 Gly Glu Leu Val Arg Glu Asn Leu Gln Val Arg Asp Met Leu Asn Glu
 130 135 140
 Val Ala Pro Leu Leu Arg Asp Asp Gly Ser Cys Met Ser Leu Asn Tyr
 145 150 155 160
 His Leu Gln Pro Val Ile Gly Val Ile Tyr Gly Pro Thr Gly Cys Gly
 165 170 175
 Lys Ser Gln Leu Leu Arg Asn Leu Leu Ser Ser Gln Leu Ile Thr Pro
 180 185 190
 Ala Pro Glu Thr Val Phe Phe Ile Ala Pro Gln Val Asp Met Ile Pro
 195 200 205
 Pro Ser Glu Met Lys Ala Trp Glu Met Gln Ile Cys Glu Gly Asn Phe
 210 215 220
 Ala Pro Gly Pro Glu Gly Thr Ile Val Pro Gln Ser Gly Thr Leu Arg
 225 230 235 240
 Pro Lys Phe Ile Lys Met Ser Tyr Asp Asp Leu Thr Gln Glu His Asn
 245 250 255
 Tyr Asp Val Ser Asp Pro Arg Asn Val Phe Ala Lys Ala Ala Ala His
 260 265 270
 Gly Pro Ile Ala Ile Ile Met Asp Glu Cys Met Glu Asn Leu Gly Gly
 275 280 285
 His Lys Gly Val Ser Lys Phe Phe His Ala Phe Pro Ser Lys Leu His
 290 295 300
 Asp Lys Phe Pro Lys Cys Thr Gly Tyr Thr Val Leu Val Val Leu His
 305 310 315 320
 Asn Met Asn Pro Arg Arg Asp Leu Gly Gly Asn Ile Ala Asn Leu Lys
 325 330 335
 Ile Gln Ala Lys Leu His Ile Ile Ser Pro Arg Met His Pro Ser Gln
 340 345 350
 Leu Asn Arg Phe Ala Asn Thr Tyr Thr Lys Gly Leu Pro Val Ala Ile
 355 360 365
 Ser Leu Leu Leu Lys Asp Ile Ile Gln His His Ala Gln Arg Pro Cys
 370 375 380
 Tyr Asp Trp Ile Ile Tyr Asn Thr Thr Pro Glu His Glu Ala Met Gln
 385 390 395 400
 Trp Cys Tyr Leu His Pro Arg Asp Gly Leu Met Pro Met Tyr Leu Asn
 405 410 415
 Ile Gln Ser His Leu Tyr Arg Val Leu Glu Lys Ile His Arg Thr Leu
 420 425 430
 Asn Asp Arg Glu Arg Trp Thr Arg Ala Tyr Arg Ala Arg Lys Asn Lys
 435 440 445

<210> SEQ ID NO 8

<211> LENGTH: 1176

<212> TYPE: PRT

<213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 8

Met Ala Leu Val Gln Ser His Gly Ala Arg Gly Leu His Ala Glu Ala
 1 5 10 15
 Ala Asp Pro Gly Cys Gln Pro Pro Arg Arg Arg Ala Arg Gln Arg Ser

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20						25						30				
Gln	Gly	Ala	Ala	Pro	Gly	Pro	Ala	Arg	Ala	Pro	Arg	Arg	Ala	Ser		
		35					40				45					
Ala	Ala	Pro	Ala	Arg	Gly	Ala	Gly	Thr	Ala	Ala	Ala	Ala	Gly	Ser	Ala	
	50					55					60					
Ser	Ala	Thr	Pro	Leu	Leu	Lys	Ala	His	Arg	Gly	Thr	Val	Val	Ala	Pro	
65				70						75				80		
Arg	Ser	Tyr	Gly	Leu	Met	Gln	Cys	Val	Asp	Thr	Ala	Thr	Asn	Ser	Pro	
				85					90					95		
Val	Glu	Ile	Lys	Tyr	His	Leu	His	Leu	Lys	His	Ala	Leu	Thr	Arg	Phe	
			100					105					110			
Tyr	Glu	Val	Asn	Leu	Arg	Thr	Leu	Pro	Pro	Asp	Leu	Asp	Leu	Arg	Asp	
		115					120					125				
Thr	Met	Asp	Ser	Ser	Gln	Leu	Arg	Ala	Leu	Val	Phe	Ala	Leu	Arg	Pro	
	130					135					140					
Arg	Arg	Ala	Glu	Ile	Trp	Thr	Trp	Leu	Pro	Arg	Gly	Leu	Val	Ser	Leu	
145					150					155					160	
Ser	Val	Leu	Glu	Glu	Pro	Gln	Gly	Glu	Ser	His	Ala	Gly	Glu	His	Glu	
				165					170					175		
Asn	His	Gln	Pro	Gly	Pro	Pro	Leu	Leu	Lys	Phe	Leu	Leu	Lys	Gly	Arg	
			180					185					190			
Ala	Val	Tyr	Leu	Val	Asp	Glu	Val	Gln	Pro	Val	Gln	Arg	Cys	Glu	Tyr	
		195					200					205				
Cys	Gly	Arg	Phe	Tyr	Lys	His	Gln	His	Glu	Cys	Ser	Val	Arg	Arg	Arg	
	210					215					220					
Asp	Phe	Tyr	Phe	His	His	Ile	Asn	Ser	His	Ser	Ser	Asn	Trp	Trp	Gln	
225					230						235				240	
Glu	Ile	Gln	Phe	Phe	Pro	Ile	Gly	Ser	His	Pro	Arg	Thr	Glu	Arg	Leu	
				245					250					255		
Phe	Val	Thr	Tyr	Asp	Val	Glu	Thr	Tyr	Thr	Trp	Met	Gly	Ser	Phe	Gly	
			260					265					270			
Lys	Gln	Leu	Val	Pro	Phe	Met	Leu	Val	Met	Lys	Phe	Ser	Gly	Asp	Pro	
		275					280					285				
Glu	Leu	Val	Ala	Leu	Ala	Arg	Asp	Leu	Ala	Val	Arg	Leu	Arg	Trp	Asp	
	290					295					300					
Arg	Trp	Glu	Arg	Asp	Pro	Leu	Thr	Phe	Tyr	Cys	Val	Thr	Pro	Glu	Lys	
305					310					315					320	
Met	Ala	Val	Gly	Gln	Gln	Phe	Arg	Leu	Phe	Arg	Asp	Glu	Leu	Gln	Thr	
				325					330					335		
Leu	Met	Ala	Arg	Glu	Leu	Trp	Ala	Ser	Phe	Met	Gln	Ala	Asn	Pro	His	
		340						345					350			
Leu	Gln	Glu	Trp	Ala	Leu	Glu	Gln	His	Gly	Leu	Gln	Cys	Pro	Glu	Asp	
		355					360					365				
Leu	Thr	Tyr	Glu	Glu	Leu	Lys	Lys	Leu	Pro	His	Ile	Lys	Gly	Arg	Pro	
	370					375					380					
Arg	Phe	Met	Glu	Leu	Tyr	Ile	Val	Gly	His	Asn	Ile	Asn	Gly	Phe	Asp	
385					390					395					400	
Glu	Ile	Val	Leu	Ala	Ala	Gln	Val	Ile	Asn	Asn	Arg	Ala	Ser	Val	Pro	
				405					410					415		
Gly	Pro	Phe	Arg	Ile	Thr	Arg	Asn	Phe	Met	Pro	Arg	Ala	Gly	Lys	Ile	
				420				425					430			
Leu	Phe	Asn	Asp	Val	Thr	Phe	Ala	Leu	Pro	Asn	Pro	Leu	Ser	Lys	Lys	
		435					440					445				

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Arg Thr Asp Phe Glu Leu Trp Glu His Gly Gly Cys Asp Asp Ser Asp																			
450						455					460								
Phe Lys Tyr Gln Phe Leu Lys Val Met Val Arg Asp Thr Phe Ala Leu																			
465					470					475									480
Thr His Thr Ser Leu Arg Lys Ala Ala Gln Ala Tyr Ala Leu Pro Val																			
				485					490										495
Glu Lys Gly Cys Cys Pro Tyr Lys Ala Val Asn His Phe Tyr Met Leu																			
			500					505						510					
Gly Ser Tyr Arg Ala Asp Asp Arg Gly Phe Pro Leu Arg Glu Tyr Trp																			
			515				520						525						
Lys Asp Asp Glu Glu Tyr Ala Leu Asn Arg Glu Leu Trp Glu Lys Lys																			
						530		535				540							
Gly Glu Ala Gly Tyr Asp Ile Ile Arg Glu Thr Leu Asp Tyr Cys Ala																			
545					550					555									560
Met Asp Val Leu Val Thr Ala Glu Leu Val Ala Lys Leu Gln Asp Ser																			
				565				570											575
Tyr Ala His Phe Ile Arg Asp Ser Val Arg Leu Pro His Ala His Phe																			
				580				585											590
Asn Ile Phe Gln Arg Pro Thr Ile Ser Ser Asn Ser His Ala Ile Phe																			
				595			600						605						
Arg Gln Ile Val Phe Arg Ala Glu Gln Pro Gln Arg Thr Asn Leu Gly																			
						610		615				620							
Pro Ala Phe Leu Ala Pro Ser His Glu Leu Tyr Asp Tyr Val Arg Ala																			
625					630					635									640
Ser Ile Arg Gly Gly Arg Cys Tyr Pro Thr Tyr Ile Gly Ile Leu Ser																			
				645				650											655
Glu Pro Ile Tyr Val Tyr Asp Ile Cys Gly Met Tyr Ala Ser Ala Leu																			
				660			665							670					
Thr His Pro Met Pro Trp Gly Pro Pro Leu Asn Pro Tyr Glu Arg Ala																			
				675			680							685					
Leu Ala Ala Arg Glu Trp Gln Met Ala Leu Asp Asp Ala Ser Ser Lys																			
				690			695					700							
Ile Asp Tyr Phe Asp Lys Glu Leu Cys Pro Gly Ile Phe Thr Ile Asp																			
705					710					715									720
Ala Asp Pro Pro Asp Glu His Leu Leu Asp Val Leu Pro Pro Phe Cys																			
				725				730											735
Ser Arg Lys Gly Gly Arg Leu Cys Trp Thr Asn Glu Pro Leu Arg Gly																			
				740			745							750					
Glu Val Ala Thr Ser Val Asp Leu Val Thr Leu His Asn Arg Gly Trp																			
				755			760							765					
Arg Val Arg Ile Val Pro Asp Glu Arg Thr Thr Val Phe Pro Glu Trp																			
				770			775							780					
Lys Cys Val Ala Arg Glu Tyr Val Gln Leu Asn Ile Ala Ala Lys Glu																			
785					790					795									800
Arg Ala Asp Arg Asp Lys Asn Gln Thr Met Arg Ser Ile Ala Lys Leu																			
				805				810											815
Leu Ser Asn Ala Leu Tyr Gly Ser Phe Ala Thr Lys Leu Asp Asn Lys																			
				820				825											830
Lys Ile Val Phe Ser Asp Gln Met Asp Glu Ser Leu Leu Lys Ser Ile																			
				835				840						845					
Ala Ala Gly Gln Ala Asn Ile Lys Ser Ser Ser Phe Leu Glu Thr Asp																			
				850			855							860					

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Asn Leu Ser Ala Glu Val Met Pro Ala Leu Glu Arg Glu Tyr Leu Pro
865                      870                      875                      880

Gln Gln Leu Ala Leu Val Asp Ser Asp Ala Glu Glu Ser Glu Asp Glu
                        885                      890                      895

His Arg Pro Ala Pro Phe Tyr Thr Pro Pro Ser Gly Thr Pro Gly His
                      900                      905                      910

Val Ala Tyr Thr Tyr Lys Pro Ile Thr Phe Leu Asp Ala Glu Glu Gly
                      915                      920                      925

Asp Met Cys Leu His Thr Val Glu Lys Val Asp Pro Leu Val Asp Asn
930                      935                      940

Asp Arg Tyr Pro Ser His Val Ala Ser Phe Val Leu Ala Trp Thr Arg
945                      950                      955                      960

Ala Phe Val Ser Glu Trp Ser Glu Phe Leu Tyr Glu Glu Asp Arg Gly
                      965                      970                      975

Thr Ser Leu Gln Asp Arg Pro Ile Lys Ser Val Tyr Gly Asp Thr Asp
                      980                      985                      990

Ser Leu Phe Val Thr Glu Arg Gly His Arg Leu Met Glu Thr Arg Gly
                      995                      1000                      1005

Lys Lys Arg Ile Lys Lys Asn Gly Gly Lys Leu Val Phe Asp Pro
1010                      1015                      1020

Glu Gln Pro Glu Leu Thr Trp Leu Val Glu Cys Glu Thr Val Cys
1025                      1030                      1035

Ala His Cys Gly Ala Asp Ala Phe Ala Pro Glu Ser Val Phe Leu
1040                      1045                      1050

Ala Pro Lys Leu Tyr Ala Leu Gln Ser Leu Leu Cys Pro Ala Cys
1055                      1060                      1065

Gly Arg Ser Ser Lys Gly Lys Leu Arg Ala Lys Gly His Ala Ala
1070                      1075                      1080

Glu Ala Leu Asn Tyr Glu Leu Met Val Asn Cys Tyr Leu Ala Asp
1085                      1090                      1095

Ala Gln Gly Glu Asp Arg Ala Arg Phe Ser Thr Ser Arg Met Ser
1100                      1105                      1110

Leu Lys Arg Thr Leu Ala Ser Ala Gln Pro Gly Ala His Pro Phe
1115                      1120                      1125

Thr Val Thr Glu Thr Thr Leu Thr Arg Thr Leu Arg Pro Trp Lys
1130                      1135                      1140

Asp Met Thr Leu Ala Ala Leu Asp Ala His Arg Leu Val Pro Tyr
1145                      1150                      1155

Ser Arg Ser Arg Pro Asn Pro Arg Asn Glu Glu Val Cys Trp Ile
1160                      1165                      1170

Glu Met Pro
1175

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<210> SEQ ID NO 9

<211> LENGTH: 129

<212> TYPE: PRT

<213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 9

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Met Arg Ala Asp Trp Glu Glu Leu Asp Phe Leu Pro Pro Val Gly Arg
1          5          10          15

Val Ala Val Asp Val Met Lys Val Glu Ile Pro Pro Ala Asn Arg Ala
                20          25          30

Leu Val Leu Met Leu Val Lys Ala Ser Ala Val Leu Ala Ala Leu His
35          40          45

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Gly Leu Tyr Leu Ile His Glu Ile His Ser Ala Ser Leu Glu Glu Glu
50 55 60

Leu Gln Glu Trp Arg Pro Trp Leu Val Val Phe Met Phe Ala Cys Val
65 70 75 80

Gly Leu Thr Leu Gly Leu Leu Glu Asp Gly Glu Ala Asp Glu Pro Ala
85 90 95

Arg Glu Pro Gly Pro Asp Leu Gly Ala Ala Gly Ala Glu Ser Glu Asp
100 105 110

Glu Gly Ala Gln Leu Gly Ala Val His Gly Val Ala Glu Ile Gln Gly
115 120 125

Thr

<210> SEQ ID NO 10
<211> LENGTH: 635
<212> TYPE: PRT
<213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 10

Met Ala Leu Ser Val Asn Asp Cys Ala Arg Leu Thr Gly Gln Thr Val
1 5 10 15

Pro Thr Met Asp Tyr Phe Leu Pro Leu Arg Asn Ile Trp Asn Arg Val
20 25 30

Arg Glu Phe Pro Arg Ala Ser Thr Thr Ala Ala Gly Ile Thr Trp Met
35 40 45

Ser Arg Tyr Leu Tyr Gly Tyr His Arg Leu Met Leu Glu Asp Leu Ala
50 55 60

Pro Gly Ala Pro Ala Thr Gln Arg Trp Pro Leu Tyr Arg Gln Pro Pro
65 70 75 80

Pro His Phe Leu Val Gly Tyr Gln Tyr Leu Val Arg Thr Cys Asn Asp
85 90 95

Tyr Val Phe Asp Ser Arg Ala Phe Ser Arg Leu Arg Tyr Ser Glu Val
100 105 110

Val Gln Pro Gly Leu Gln Thr Val Asn Trp Ser Leu Met Ala Asn Cys
115 120 125

Thr Tyr Thr Ile Asn Thr Gly Ala Tyr His Arg Phe Val Asp Met Asp
130 135 140

Asp Phe Gln Asp Thr Leu Thr Arg Val Gln Gln Ala Ile Leu Ala Glu
145 150 155 160

Arg Val Val Ala Asp Leu Ala Leu Val Gln Pro Leu Arg Gly Val Gly
165 170 175

Val Thr Arg Met Glu Asp Ser Ala Ser Ala Ser Asp Asp Ile Glu Arg
180 185 190

Leu Met His Asp Tyr Tyr Lys Asn Leu Ser Arg Cys Gln Gly Gln Ala
195 200 205

Trp Gly Met Ala Glu Arg Leu Arg Ile Gln Gln Ala Gly Pro Lys Asp
210 215 220

Leu Val Leu Leu Ala Thr Ile Arg Arg Leu Lys Asn Ala Tyr Phe Asn
225 230 235 240

Tyr Ile Ile Ser Asn Arg Asn Ser Asn Ser Val His Arg Ala Ala Thr
245 250 255

Cys Leu Ser Leu Pro Cys Asp Cys Asp Trp Leu Asp Ala Phe Leu Glu
260 265 270

Arg Phe Ser Asp Pro Val Asp Leu Asp Ala Leu Thr Ser Pro Thr Pro
275 280 285

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Gln Leu Ile Arg Cys Ile Val Ser Ala Leu Ser Leu Pro Asn Gly Asp
 290 295 300
 Pro Pro His Tyr Arg Glu Met Thr Gly Gly Val Phe Thr Leu Arg Pro
 305 310 315 320
 Arg Glu Arg Gly Arg Ala Val Thr Glu Thr Met Arg Arg Arg Arg Gly
 325 330 335
 Glu Met Ile Glu Arg Phe Val Asp Arg Leu Pro Val Arg Arg Arg Arg
 340 345 350
 Arg Arg Ala Pro Pro Pro Pro Pro Pro Glu Glu Glu Ile Glu Glu
 355 360 365
 Glu Val Val Met Glu Glu Glu Glu Glu Glu Val Pro Gly Asp Phe
 370 375 380
 Glu Arg Glu Val Arg Ala Thr Ile Ala Glu Leu Ile Arg Leu Leu Glu
 385 390 395 400
 Asp Glu Leu Thr Val Ser Ala Arg Asn Ala Gln Phe Phe Asn Phe Ala
 405 410 415
 Val Asp Phe Tyr Glu Ala Met Glu Arg Leu Glu Ala Ile Gly Asp Ile
 420 425 430
 Ser Glu Met Pro Leu Arg Arg Trp Ile Met Tyr Phe Phe Val Thr Glu
 435 440 445
 His Ile Ala Thr Thr Leu Asn Tyr Leu Phe Gln Arg Leu Arg Asn Tyr
 450 455 460
 Ala Val Phe Thr Arg His Val Glu Leu Asn Leu Ala Gln Val Val Met
 465 470 475 480
 Arg Ala Arg Asp Ala Asp Gly Asp Val Val Tyr Ser Arg Val Trp Asn
 485 490 495
 Glu Ser Gly Leu Gly Ala Phe Ser Gln Leu Met Gly Arg Ile Ser Asn
 500 505 510
 Asp Leu Ala Ala Thr Val Glu Arg Ala Gly Arg Gly Asp Leu Gln Glu
 515 520 525
 Glu Glu Ile Glu Gln Phe Met Ser Glu Ile Ala Tyr Gln Asp Asn Ser
 530 535 540
 Gly Asp Val Gln Glu Ile Leu Arg Gln Ala Ala Val Asn Asp Ala Glu
 545 550 555 560
 Ile Asp Ser Val Glu Leu Ser Phe Arg Phe Lys Val Thr Gly Pro Val
 565 570 575
 Val Phe Thr Gln Arg Arg Gln Ile Gln Asp Val Asn Arg Arg Val Val
 580 585 590
 Ala His Ala Ser Ala Leu Arg Ala Gln His Arg Asp Leu Pro Glu Arg
 595 600 605
 His Ala Asp Val Pro Leu Pro Pro Leu Pro Ala Gly Pro Glu Pro Pro
 610 615 620
 Leu Pro Pro Gly Ala Arg Pro Arg His Arg Phe
 625 630 635

<210> SEQ ID NO 11

<211> LENGTH: 372

<212> TYPE: PRT

<213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 11

Met His Pro Val Leu Arg Gln Met Arg Pro Thr Pro Pro Ala Thr Thr
 1 5 10 15

Ala Thr Ala Ala Val Thr Gly Ala Gly Ala Ser Gln Pro Gln Thr Glu

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20					25					30				
Met	Asp	Leu	Glu	Gly	Glu	Gly	Leu	Ala	Arg	Leu	Gly	Ala	Pro	Ser
	35					40					45			
Pro	Glu	Arg	His	Pro	Arg	Val	Gln	Leu	Gln	Lys	Asp	Val	Arg	Pro
	50					55					60			Ala
Tyr	Val	Pro	Ala	Gln	Asn	Leu	Phe	Arg	Asp	Arg	Ser	Gly	Glu	Pro
	65					70					75			80
Glu	Glu	Met	Arg	Asp	Cys	Arg	Phe	Arg	Ala	Gly	Arg	Glu	Leu	Arg
			85						90				95	Glu
Gly	Leu	Asp	Arg	Gln	Arg	Val	Leu	Arg	Asp	Glu	Asp	Phe	Glu	Pro
		100						105					110	Asn
Glu	Gln	Thr	Gly	Ile	Ser	Pro	Ala	Arg	Ala	His	Val	Ala	Ala	Ala
		115						120					125	Asn
Leu	Val	Thr	Ala	Tyr	Glu	Gln	Thr	Val	Lys	Gln	Glu	Arg	Asn	Phe
	130						135					140		Gln
Lys	Ser	Phe	Asn	Asn	His	Val	Arg	Thr	Leu	Ile	Ala	Arg	Glu	Glu
	145					150					155			160
Ala	Leu	Gly	Leu	Met	His	Leu	Trp	Asp	Leu	Ala	Glu	Ala	Ile	Val
			165						170				175	Gln
Asn	Pro	Asp	Ser	Lys	Pro	Leu	Thr	Ala	Gln	Leu	Phe	Leu	Val	Gln
		180						185					190	
His	Ser	Arg	Asp	Asn	Glu	Ala	Phe	Arg	Glu	Ala	Leu	Leu	Asn	Ile
		195					200					205		Ala
Glu	Pro	Glu	Gly	Arg	Trp	Leu	Leu	Glu	Leu	Ile	Asn	Ile	Leu	Gln
	210					215					220			Ser
Ile	Val	Val	Gln	Glu	Arg	Ser	Leu	Ser	Leu	Ala	Glu	Lys	Val	Ala
	225					230					235			240
Ile	Asn	Tyr	Ser	Val	Leu	Ser	Leu	Gly	Lys	Phe	Tyr	Ala	Arg	Lys
			245						250				255	Ile
Tyr	Lys	Thr	Pro	Tyr	Val	Pro	Ile	Asp	Lys	Glu	Val	Lys	Ile	Asp
		260						265					270	Ser
Phe	Tyr	Met	Arg	Met	Ala	Leu	Lys	Val	Leu	Thr	Leu	Ser	Asp	Asp
		275					280					285		Leu
Gly	Val	Tyr	Arg	Asn	Asp	Arg	Ile	His	Lys	Ala	Val	Ser	Thr	Ser
	290					295					300			Arg
Arg	Arg	Glu	Leu	Ser	Asp	Arg	Glu	Leu	Met	Leu	Ser	Leu	Arg	Arg
	305					310					315			320
Leu	Val	Gly	Gly	Ala	Ala	Gly	Gly	Glu	Glu	Ser	Tyr	Phe	Asp	Met
			325					330					335	Gly
Ala	Asp	Leu	His	Trp	Gln	Pro	Ser	Arg	Arg	Ala	Leu	Glu	Ala	Tyr
		340						345					350	
Gly	Pro	Glu	Asp	Leu	Asp	Glu	Asp	Glu	Glu	Glu	Glu	Glu	Asp	Ala
	355					360						365		Pro
Val	Ala	Gly	Tyr											
	370													

<210> SEQ ID NO 12

<211> LENGTH: 561

<212> TYPE: PRT

<213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 12

Met	Ser	Gln	Gln	Ala	Pro	Asp	Pro	Ala	Ile	Arg	Ala	Ala	Leu	Gln	Ser
1				5					10					15	

Gln	Pro	Ser	Gly 20	Leu	Ala	Ser	Asp	Asp 25	Trp	Glu	Ala	Ala	Met 30	Gln	Arg
Ile	Met	Ala 35	Leu	Thr	Thr	Arg	Asn 40	Pro	Glu	Ser	Phe	Arg 45	Gln	Gln	Pro
Gln	Ala 50	Asn	Arg	Leu	Ser	Ala 55	Ile	Leu	Glu	Ala	Val 60	Val	Pro	Ser	Arg
Thr 65	Asn	Pro	Thr	His	Glu 70	Lys	Val	Leu	Ala	Ile 75	Val	Asn	Ala	Leu	Ala 80
Glu	Asn	Lys	Ala	Ile 85	Arg	Pro	Asp	Glu	Ala 90	Gly	Leu	Val	Tyr	Asn 95	Ala
Leu	Leu	Glu	Arg 100	Val	Gly	Arg	Tyr	Asn 105	Ser	Thr	Asn	Val	Gln 110	Ser	Asn
Leu	Asp 115	Arg	Leu	Val	Thr	Asp	Val 120	Arg	Glu	Ala	Val	Ala 125	Gln	Arg	Glu
Arg	Phe 130	Lys	Asn	Glu	Gly	Leu 135	Gly	Ser	Leu	Val	Ala 140	Leu	Asn	Ala	Phe
Leu 145	Ala	Thr	Gln	Pro	Ala 150	Asn	Val	Pro	Arg	Gly 155	Gln	Asp	Asp	Tyr	Thr 160
Asn	Phe	Ile	Ser	Ala 165	Leu	Arg	Leu	Met	Val 170	Thr	Glu	Val	Pro	Gln 175	Ser
Glu	Val	Tyr	Gln 180	Ser	Gly	Pro	Asp	Tyr 185	Phe	Phe	Gln	Thr	Ser 190	Arg	Gln
Gly	Leu 195	Gln	Thr	Val	Asn	Leu	Ser 200	Gln	Ala	Phe	Lys	Asn 205	Leu	Arg	Gly
Leu	Trp 210	Gly	Val	Gln	Ala	Pro 215	Val	Gly	Asp	Arg	Ser 220	Thr	Val	Ser	Ser
Leu 225	Leu	Thr	Pro	Asn	Ser 230	Arg	Leu	Leu	Leu	Leu 235	Leu	Ile	Ala	Pro	Phe 240
Thr	Asp	Ser	Gly 245	Ser	Val	Asn	Arg	Asn 250	Ser	Tyr	Leu	Gly	His 255	Leu	Leu
Thr	Leu	Tyr	Arg 260	Glu	Ala	Ile	Gly	Gln 265	Ala	Gln	Val	Asp 270	Glu	Gln	Thr
Phe	Gln	Glu 275	Ile	Thr	Ser	Val	Ser 280	Arg	Ala	Leu	Gly	Gln 285	Asn	Asp	Thr
Asp	Ser 290	Leu	Arg	Ala	Thr	Leu 295	Asn	Phe	Leu	Leu	Thr 300	Asn	Arg	Gln	Gln
Lys 305	Ile	Pro	Ala	Gln	Tyr 310	Ala	Leu	Ser	Ala	Glu 315	Glu	Glu	Arg	Ile	Leu 320
Arg	Tyr	Val	Gln 325	Gln	Ser	Val	Gly	Leu	Phe 330	Leu	Met	Gln	Glu	Gly 335	Ala
Thr	Pro	Ser	Ala 340	Ala	Leu	Asp	Met	Thr 345	Ala	Arg	Asn	Met 350	Glu	Pro	Ser
Met	Tyr	Ala 355	Ala	Asn	Arg	Pro	Phe 360	Ile	Asn	Lys	Leu	Met 365	Asp	Tyr	Leu
His 370	Arg	Ala	Ala	Ala	Met	Asn 375	Thr	Asp	Tyr	Phe	Thr 380	Asn	Ala	Ile	Leu
Asn 385	Pro	His	Trp	Leu	Pro 390	Pro	Pro	Gly	Phe	Tyr 395	Thr	Gly	Glu	Tyr	Asp 400
Met	Pro	Asp	Pro	Asn 405	Asp	Gly	Phe	Leu	Trp 410	Asp	Asp	Val	Asp	Ser	Ala 415
Val	Phe	Ser	Pro 420	Thr	Phe	Gln	Lys	Arg 425	Gln	Glu	Ala	Pro 430	Pro	Ser	Glu
Gly	Ala	Val	Gly	Arg	Ser	Pro	Phe	Pro	Ser	Leu	Gly	Ser	Leu	His	Ser

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435	440	445
Leu Pro Gly Ser Val Asn Ser Gly Arg Val Ser Arg Pro Arg Leu Leu		
450	455	460
Gly Glu Asp Glu Tyr Leu Asn Asp Ser Leu Leu Gln Pro Pro Arg Val		
465	470	475
Lys Asn Ala Met Ala Asn Asn Gly Ile Glu Ser Leu Val Asp Lys Leu		
	485	490
Asn Arg Trp Lys Thr Tyr Ala Gln Asp His Arg Glu Pro Ala Pro Ala		
	500	505
Pro Arg Arg Gln Arg His Asp Arg Gln Arg Gly Leu Val Trp Asp Asp		
	515	520
Glu Asp Ser Ala Asp Asp Ser Ser Val Leu Asp Leu Gly Gly Ser Gly		
530	535	540
Gly Ala Asn Pro Phe Ala His Leu Gln Pro Arg Leu Gly Arg Arg Met		
545	550	555

Phe

<210> SEQ ID NO 13

<211> LENGTH: 520

<212> TYPE: PRT

<213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 13

Met Arg Arg Ala Val Val Ser Ser Ser Pro Pro Pro Ser Tyr Glu Ser		
1	5	10
Val Met Ala Gln Ala Thr Leu Glu Val Pro Phe Val Pro Pro Arg Tyr		
	20	25
Met Ala Pro Thr Glu Gly Arg Asn Ser Ile Arg Tyr Ser Glu Leu Ala		
	35	40
Pro Gln Tyr Asp Thr Thr Arg Val Tyr Leu Val Asp Asn Lys Ser Ala		
	50	55
Asp Ile Ala Ser Leu Asn Tyr Gln Asn Asp His Ser Asn Phe Leu Thr		
65	70	75
Thr Val Val Gln Asn Asn Asp Phe Thr Pro Ala Glu Ala Ser Thr Gln		
	85	90
Thr Ile Asn Phe Asp Glu Arg Ser Arg Trp Gly Gly Asp Leu Lys Thr		
	100	105
Ile Leu His Thr Asn Met Pro Asn Val Asn Glu Tyr Met Phe Thr Ser		
	115	120
Lys Phe Lys Ala Arg Val Met Val Ala Arg Lys His Pro Lys Asp Val		
	130	135
Asp Ala Ser Asp Leu Ser Lys Asp Ile Leu Glu Tyr Lys Trp Phe Glu		
145	150	155
Phe Thr Leu Pro Glu Gly Asn Phe Ser Glu Thr Met Thr Ile Asp Leu		
	165	170
Met Asn Asn Ala Ile Leu Glu Asn Tyr Leu Gln Val Gly Arg Gln Asn		
	180	185
Gly Val Leu Glu Ser Asp Ile Gly Val Lys Phe Asp Ser Arg Asn Phe		
	195	200
Arg Leu Gly Trp Asp Pro Val Thr Lys Leu Val Met Pro Gly Val Tyr		
	210	215
Thr Tyr Glu Ala Phe His Pro Asp Val Val Leu Leu Pro Gly Cys Gly		
225	230	235
Val Asp Phe Thr Glu Ser Arg Leu Ser Asn Leu Leu Gly Ile Arg Lys		

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245																250				255			
Lys	Gln	Pro	Phe	Gln	Glu	Gly	Phe	Arg	Ile	Met	Tyr	Glu	Asp	Leu	Glu								
			260						265				270										
Gly	Gly	Asn	Ile	Pro	Ala	Leu	Leu	Asp	Thr	Lys	Lys	Tyr	Leu	Asp	Ser								
			275						280				285										
Lys	Lys	Glu	Leu	Glu	Asp	Ala	Ala	Lys	Glu	Ala	Ala	Lys	Gln	Gln	Gly								
			290						295				300										
Asp	Gly	Ala	Val	Thr	Arg	Gly	Asp	Thr	His	Leu	Thr	Val	Ala	Gln	Glu								
			305						310				315										
Lys	Ala	Ala	Glu	Lys	Glu	Leu	Val	Ile	Val	Pro	Ile	Glu	Lys	Asp	Glu								
			325						330				335										
Ser	Asn	Arg	Ser	Tyr	Asn	Leu	Ile	Lys	Asp	Thr	His	Asp	Thr	Leu	Tyr								
			340						345				350										
Arg	Ser	Trp	Tyr	Leu	Ser	Tyr	Thr	Tyr	Gly	Asp	Pro	Glu	Lys	Gly	Val								
			355						360				365										
Gln	Ser	Trp	Thr	Leu	Leu	Thr	Thr	Pro	Asp	Val	Thr	Cys	Gly	Ala	Glu								
			370						375				380										
Gln	Val	Tyr	Trp	Ser	Leu	Pro	Asp	Leu	Met	Gln	Asp	Pro	Val	Thr	Phe								
			385						390				395										
Arg	Ser	Thr	Gln	Gln	Val	Ser	Asn	Tyr	Pro	Val	Val	Gly	Ala	Glu	Leu								
			405						410				415										
Met	Pro	Phe	Arg	Ala	Lys	Ser	Phe	Tyr	Asn	Asp	Leu	Ala	Val	Tyr	Ser								
			420						425				430										
Gln	Leu	Ile	Arg	Ser	Tyr	Thr	Ser	Leu	Thr	His	Val	Phe	Asn	Arg	Phe								
			435						440				445										
Pro	Asp	Asn	Gln	Ile	Leu	Cys	Arg	Pro	Pro	Ala	Pro	Thr	Ile	Thr	Thr								
			450						455				460										
Val	Ser	Glu	Asn	Val	Pro	Ala	Leu	Thr	Asp	His	Gly	Thr	Leu	Pro	Leu								
			465						470				475										
Arg	Ser	Ser	Ile	Arg	Gly	Val	Gln	Arg	Val	Thr	Val	Thr	Asp	Ala	Arg								
			485						490				495										
Arg	Arg	Thr	Cys	Pro	Tyr	Val	Tyr	Lys	Ala	Leu	Gly	Ile	Val	Ala	Pro								
			500						505				510										
Arg	Val	Leu	Ser	Ser	Arg	Thr	Phe																
			515						520														
<210> SEQ ID NO 14																							
<211> LENGTH: 195																							
<212> TYPE: PRT																							
<213> ORGANISM: Adenovirus type 36																							
<400> SEQUENCE: 14																							
Met	Ser	Ile	Leu	Ile	Ser	Pro	Ser	Asn	Asn	Thr	Gly	Trp	Gly	Leu	Thr								
1				5						10				15									
Arg	Pro	Ser	Thr	Met	Tyr	Gly	Gly	Ala	Lys	Lys	Arg	Ser	Gln	Gln	His								
			20						25				30										
Pro	Val	Arg	Val	Arg	Gly	His	Phe	Arg	Ala	Pro	Trp	Gly	Ala	Tyr	Lys								
			35						40				45										
Arg	Gly	Arg	Thr	Ala	Thr	Ala	Ala	Ala	Val	Arg	Thr	Thr	Val	Asp	Asp								
			50						55				60										
Val	Ile	Asp	Ser	Val	Val	Ala	Asp	Ala	Arg	Asn	Tyr	Thr	Pro	Ala	Pro								
			65						70				75										
Ser	Thr	Val	Asp	Ala	Val	Ile	Asp	Ser	Val	Val	Ala	Asp	Ala	Arg	Asp								
			85						90				95										

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Tyr Ala Arg Arg Lys Ser Arg Arg Arg Arg Ile Ala Arg Arg His Arg
 100 105 110
 Ser Thr Pro Ala Met Arg Ala Ala Arg Ala Leu Leu Arg Arg Ala Arg
 115 120 125
 Arg Thr Gly Arg Arg Ala Met Met Arg Ala Ala Arg Arg Ala Ala Thr
 130 135 140
 Ala Pro Pro Ala Gly Arg Thr Arg Arg Arg Ala Ala Ala Ala Ala
 145 150 155 160
 Ala Ala Ile Ser Ser Met Thr Arg Pro Arg Arg Gly Asn Val Tyr Trp
 165 170 175
 Val Arg Asp Ser Val Thr Gly Val Arg Val Pro Val Arg Thr Arg Pro
 180 185 190
 Pro Arg Pro
 195

<210> SEQ ID NO 15
 <211> LENGTH: 332
 <212> TYPE: PRT
 <213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 15

Met Ser Lys Arg Lys Ile Lys Glu Glu Met Leu Gln Val Val Ala Pro
 1 5 10 15
 Glu Ile Tyr Gly Pro Pro Asp Gln Lys Pro Arg Lys Ile Lys Arg Val
 20 25 30
 Lys Lys Lys Asp Glu Val Asp Glu Gly Ala Val Glu Phe Val Arg Glu
 35 40 45
 Phe Ala Pro Arg Arg Arg Val Asn Trp Lys Gly Arg Arg Val Gln Arg
 50 55 60
 Val Leu Arg Pro Gly Thr Ala Val Val Phe Thr Pro Gly Glu Arg Ser
 65 70 75 80
 Ser Val Arg Ser Lys Arg Ser Tyr Asp Glu Val Tyr Gly Asp Asp Asp
 85 90 95
 Ile Leu Asp Gln Ala Ala Glu Arg Ala Gly Glu Phe Ala Tyr Gly Lys
 100 105 110
 Arg Ser Arg Glu Glu Glu Leu Ile Ser Leu Pro Leu Asp Glu Ser Asn
 115 120 125
 Pro Thr Pro Ser Leu Lys Pro Val Thr Leu Gln Gln Val Leu Pro Gln
 130 135 140
 Ala Val Leu Leu Pro Ser Arg Gly Val Lys Arg Glu Gly Glu Ser Met
 145 150 155 160
 Tyr Pro Thr Met Gln Ile Met Val Pro Lys Arg Arg Arg Val Glu Asp
 165 170 175
 Val Leu Asp Thr Val Lys Met Asp Val Glu Pro Glu Val Lys Val Arg
 180 185 190
 Pro Ile Lys Gln Val Ala Pro Gly Leu Gly Val Gln Thr Val Asp Ile
 195 200 205
 Gln Ile Pro Thr Asp Met Asp Val Asp Lys Lys Pro Ser Thr Ser Ile
 210 215 220
 Glu Val Gln Thr Asp Pro Trp Leu Pro Ala Ser Thr Ala Thr Val Ser
 225 230 235 240
 Thr Phe Thr Ala Ala Thr Ala Thr Glu Pro Pro Arg Arg Arg Arg Trp
 245 250 255
 Gly Ala Ala Ser Arg Leu Met Pro Asn Tyr Val Leu His Pro Ser Ile
 260 265 270

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Ile Pro Thr Pro Gly Tyr Arg Gly Thr Arg Tyr Tyr Ala Ser Arg Arg
    275                280                285

Arg Pro Ala Ala Lys Arg Arg Arg Arg Thr Ala Thr Arg Arg Arg Leu
    290                295                300

Ala Pro Ala Arg Val Arg Arg Val Thr Thr Arg Arg Gly Arg Ser Leu
    305                310                315                320

Val Leu Pro Thr Val Arg Tyr His Pro Ser Ile Leu
    325                330

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<210> SEQ ID NO 16
<211> LENGTH: 74
<212> TYPE: PRT
<213> ORGANISM: Adenovirus type 36

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<400> SEQUENCE: 16

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Met Ala Leu Thr Cys Arg Leu Arg Ile Pro Val Pro Asn Tyr Arg Gly
 1          5          10          15

Arg Ser Arg Arg Arg Arg Gly Met Ala Gly Ser Gly Leu Asn Arg Arg
 20          25          30

Arg Arg Arg Ala Met Arg Arg Arg Leu Ser Gly Gly Phe Leu Pro Ala
 35          40          45

Leu Ile Pro Ile Ile Ala Ala Ala Ile Gly Thr Ile Pro Gly Ile Ala
 50          55          60

Ser Val Ala Leu Gln Ala Ser Gln Arg Arg
 65          70

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<210> SEQ ID NO 17
<211> LENGTH: 234
<212> TYPE: PRT
<213> ORGANISM: Adenovirus type 36

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<400> SEQUENCE: 17

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Met Glu Asp Ile Asn Phe Ala Ser Leu Ala Pro Arg His Gly Thr Arg
 1          5          10          15

Pro Phe Met Gly Thr Trp Asn Glu Ile Gly Thr Ser Gln Leu Asn Gly
 20          25          30

Gly Ala Phe Asn Trp Ser Ser Val Trp Ser Gly Leu Lys Asn Phe Gly
 35          40          45

Ser Thr Leu Arg Thr Tyr Gly Asn Lys Ala Trp Asn Ser Ser Thr Gly
 50          55          60

Gln Leu Leu Arg Glu Lys Leu Lys Asp Gln Asn Phe Gln Gln Lys Val
 65          70          75          80

Val Asp Gly Leu Ala Ser Gly Ile Asn Gly Val Val Asp Ile Ala Asn
 85          90          95

Gln Ala Val Gln Arg Glu Ile Asn Ser Arg Leu Asp Pro Arg Pro Pro
100          105          110

Thr Val Val Glu Met Glu Asp Ala Thr Leu Pro Pro Pro Lys Gly Glu
115          120          125

Lys Arg Pro Arg Pro Asp Ala Glu Glu Thr Ile Leu Gln Val Asp Glu
130          135          140

Pro Pro Ser Tyr Glu Glu Ala Val Lys Ala Gly Met Pro Thr Thr Arg
145          150          155          160

Ile Ile Ala Pro Leu Ala Thr Gly Val Met Lys Pro Ala Thr Leu Asp
165          170          175

Leu Pro Pro Pro Pro Thr Pro Ala Pro Pro Lys Ala Ala Pro Val Val
180          185          190

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Gln Ala Pro Pro Val Ala Thr Ala Val Arg Arg Val Pro Ala Arg Arg
 195 200 205

Gln Ala Gln Asn Trp Gln Ser Thr Leu His Ser Ile Val Gly Leu Gly
 210 215 220

Val Lys Ser Leu Lys Arg Arg Arg Cys Tyr
 225 230

<210> SEQ ID NO 18
 <211> LENGTH: 944
 <212> TYPE: PRT
 <213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 18

Met Ala Thr Pro Ser Met Met Pro Gln Trp Ala Tyr Met His Ile Ala
 1 5 10 15

Gly Gln Asp Ala Ser Glu Tyr Leu Ser Pro Gly Leu Val Gln Phe Ala
 20 25 30

Arg Ala Thr Asp Thr Tyr Phe Ser Leu Gly Asn Lys Phe Arg Asn Pro
 35 40 45

Thr Val Ala Pro Thr His Asp Val Thr Thr Asp Arg Ser Gln Arg Leu
 50 55 60

Thr Leu Arg Phe Val Pro Val Asp Arg Glu Asp Thr Thr Tyr Ser Tyr
 65 70 75 80

Lys Ala Arg Phe Thr Leu Ala Val Gly Asp Asn Arg Val Leu Asp Met
 85 90 95

Ala Ser Thr Tyr Phe Asp Ile Arg Gly Val Leu Asp Arg Gly Pro Ser
 100 105 110

Phe Lys Pro Tyr Ser Gly Thr Ala Tyr Asn Ser Leu Ala Pro Lys Gly
 115 120 125

Ala Pro Asn Ser Ser Gln Trp Thr Asp Lys Glu Arg Gln Asn Gly Gly
 130 135 140

Gln Pro Pro Thr Thr Lys Asp Val Thr Lys Thr Phe Gly Val Ala Ala
 145 150 155 160

Arg Gly Gly Leu His Ile Thr Asp Lys Gly Leu Gln Ile Gly Glu Asp
 165 170 175

Glu Asn Asn Glu Asp Gly Glu Glu Glu Ile Tyr Ala Asp Lys Thr Phe
 180 185 190

Gln Pro Glu Pro Gln Val Gly Glu Glu Asn Trp Gln Asp Thr Asp Val
 195 200 205

Phe Tyr Gly Gly Arg Ala Leu Lys Lys Glu Thr Lys Met Lys Pro Cys
 210 215 220

Tyr Gly Ser Phe Ala Arg Pro Thr Asn Glu Lys Gly Gly Gln Ala Lys
 225 230 235 240

Phe Leu Asn Gly Glu Asn Gly Gln Pro Ser Lys Asp Gln Asp Ile Thr
 245 250 255

Leu Ala Phe Phe Asp Leu Lys Gln Asn Asp Thr Gly Thr Thr Gln Asn
 260 265 270

Gln Pro Asp Val Val Met Tyr Thr Glu Asn Val Tyr Leu Glu Thr Pro
 275 280 285

Asp Thr His Val Val Tyr Lys Pro Gly Lys Glu Asp Thr Ser Ser Ala
 290 295 300

Ala Asn Leu Thr Gln Gln Ser Met Pro Asn Arg Pro Asn Tyr Ile Gly
 305 310 315 320

Phe Arg Asp Asn Phe Val Gly Leu Met Tyr Tyr Asn Ser Thr Gly Asn

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325																330																335															
Met	Gly	Val	Leu			Ala	Gly	Gln	Ala	Ser	Gln	Leu	Asn	Ala	Val	Val	Asp																														
340																345																350															
Leu	Gln	Asp	Arg	Asn	Thr	Glu	Leu	Ser	Tyr	Gln	Leu	Leu	Leu	Leu	Asp	Ser																															
355																360																365															
Leu	Gly	Asp	Arg	Thr	Arg	Tyr	Phe	Ser	Met	Trp	Asn	Ser	Ala	Val	Asp																																
370																375																380															
Ser	Tyr	Asp	Pro	Asp	Val	Arg	Ile	Ile	Glu	Asn	His	Gly	Val	Glu	Asp																																
385																390																395															
Glu	Leu	Pro	Asn	Tyr	Cys	Phe	Pro	Leu	Asp	Gly	Ser	Gly	Ser	Asn	Thr																																
405																410																415															
Ala	Tyr	Gln	Gly	Val	Lys	Tyr	Glu	Asn	Gly	Ala	Gly	Asn	Gly	Ser	Trp																																
420																425																430															
Lys	Val	Asp	Gly	Glu	Val	Ala	Ser	Gln	Asn	Gln	Ile	Ala	Lys	Gly	Asn																																
435																440																445															
Leu	Tyr	Ala	Met	Glu	Ile	Asn	Leu	Gln	Ala	Asn	Leu	Trp	Lys	Ser	Phe																																
450																455																460															
Leu	Tyr	Ser	Asn	Val	Ala	Leu	Tyr	Leu	Pro	Asp	Ser	Tyr	Lys	Tyr	Thr																																
465																470																475															
Pro	Ala	Asn	Ile	Thr	Leu	Pro	Thr	Asn	Thr	Asn	Thr	Tyr	Glu	Tyr	Met																																
485																490																495															
Asn	Gly	Arg	Val	Val	Ala	Pro	Ser	Leu	Val	Asp	Ala	Tyr	Val	Asn	Ile																																
500																505																510															
Gly	Ala	Arg	Trp	Ser	Leu	Asp	Pro	Met	Asp	Asn	Val	Asn	Pro	Phe	Asn																																
515																520																525															
His	His	Arg	Asn	Ala	Gly	Leu	Arg	Tyr	Arg	Ser	Met	Leu	Leu	Gly	Asn																																
530																535																540															
Gly	Arg	Tyr	Val	Pro	Phe	His	Ile	Gln	Val	Pro	Gln	Lys	Phe	Phe	Ala																																
545																550																555															
Ile	Lys	Asn	Leu	Leu	Leu	Leu	Pro	Gly	Ser	Tyr	Thr	Tyr	Glu	Trp	Asn																																
565																570																575															
Phe	Arg	Lys	Asp	Val	Asn	Met	Ile	Leu	Gln	Ser	Ser	Leu	Gly	Asn	Asp																																
580																585																590															
Leu	Arg	Val	Asp	Gly	Ala	Ser	Val	Arg	Phe	Asp	Ser	Val	Asn	Leu	Tyr																																
595																600																605															
Ala	Thr	Phe	Phe	Pro	Met	Ala	His	Asn	Thr	Ala	Ser	Thr	Leu	Glu	Ala																																
610																615																620															
Met	Leu	Arg	Asn	Asp	Thr	Asn	Asp	Gln	Ser	Phe	Asn	Asp	Tyr	Leu	Ser																																
625																630																635															
Ala	Ala	Asn	Met	Leu	Tyr	Pro	Ile	Pro	Ala	Lys	Ala	Thr	Asn	Val	Pro																																
645																650																655															
Ile	Ser	Ile	Pro	Ser	Arg	Asn	Trp	Ala	Ala	Phe	Arg	Gly	Trp	Ser	Phe																																
660																665																670															
Thr	Arg	Leu	Lys	Thr	Lys	Glu	Thr	Pro	Ser	Leu	Gly	Ser	Gly	Phe	Asp																																
675																680																685															
Pro	Tyr	Phe	Val	Tyr	Ser	Gly	Ser	Ile	Pro	Tyr	Leu	Asp	Gly	Thr	Phe																																
690																695																700															
Tyr	Leu	Asn	His	Thr	Phe	Lys	Lys	Val	Ser	Ile	Met	Phe	Asp	Ser	Ser																																
705																710																715															
Val	Ser	Trp	Pro	Gly	Asn	Asp	Arg	Leu	Leu	Thr	Pro	Asn	Glu	Phe	Glu																																
725																730																735															
Ile	Lys	Arg	Ser	Val	Asp	Gly	Glu	Gly	Tyr	Asn	Val	Ala	Gln	Cys	Asn																																
740																745																750															

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Met Thr Lys Asp Trp Phe Leu Val Gln Met Leu Ser His Tyr Asn Ile
755 760 765

Gly Tyr Gln Gly Phe Tyr Val Pro Glu Gly Tyr Lys Asp Arg Met Tyr
770 775 780

Ser Phe Phe Arg Asn Phe Gln Pro Met Ser Arg Gln Val Val Asp Glu
785 790 795 800

Ile Asn Tyr Lys Asp Tyr Lys Ala Val Thr Leu Pro Phe Gln His Asn
805 810 815

Asn Ser Gly Phe Thr Gly Tyr Leu Ala Pro Thr Met Arg Gln Gly Gln
820 825 830

Pro Tyr Pro Ala Asn Phe Pro Tyr Pro Leu Ile Gly Gln Thr Ala Val
835 840 845

Pro Ser Val Thr Gln Lys Lys Phe Leu Cys Asp Arg Val Met Trp Arg
850 855 860

Ile Pro Phe Ser Ser Asn Phe Met Ser Met Gly Ala Leu Thr Asp Leu
865 870 875 880

Gly Gln Asn Met Leu Tyr Ala Asn Ser Ala His Ala Leu Asp Met Thr
885 890 895

Phe Glu Val Asp Pro Met Asp Glu Pro Thr Leu Leu Tyr Leu Leu Phe
900 905 910

Glu Val Phe Asp Val Val Arg Val His Gln Pro His Arg Gly Val Ile
915 920 925

Glu Ala Val Tyr Leu Arg Thr Pro Phe Ser Ala Gly Asn Ala Thr Thr
930 935 940

<210> SEQ ID NO 19

<211> LENGTH: 209

<212> TYPE: PRT

<213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 19

Met Ser Gly Ser Ser Glu Arg Glu Leu Ala Ala Ile Val Arg Asp Leu
1 5 10 15

Gly Cys Gly Pro Tyr Phe Leu Gly Thr His Asp Lys Arg Phe Pro Gly
20 25 30

Phe Leu Ala Gly Asp Lys Leu Ala Cys Ala Ile Val Asn Thr Ala Gly
35 40 45

Arg Glu Thr Gly Gly Val His Trp Leu Ala Phe Gly Trp Asn Pro Arg
50 55 60

Ser Arg Thr Cys Tyr Met Phe Asp Pro Phe Gly Phe Ser Asp Arg Arg
65 70 75 80

Leu Lys Gln Ile Tyr Ser Phe Glu Tyr Glu Ala Met Leu Arg Arg Ser
85 90 95

Ala Leu Ala Ser Ser Pro Asp Arg Cys Leu Ser Leu Glu Gln Ser Thr
100 105 110

Gln Thr Val Gln Gly Pro Asp Ser Ala Ala Cys Gly Leu Phe Cys Cys
115 120 125

Met Phe Leu His Ala Phe Val His Trp Pro Asp Arg Pro Met Asp Gly
130 135 140

Asn Pro Thr Met Asn Leu Leu Thr Gly Val Pro Asn Gly Met Leu Gln
145 150 155 160

Ser Pro Gln Val Leu Pro Thr Leu Arg Arg Asn Gln Glu Glu Leu Tyr
165 170 175

Arg Phe Leu Ala Arg His Ser Pro Tyr Phe Arg Ser His Arg Ala Ala

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180	185	190
Ile Glu His Ala Thr Ala Phe Asp Lys Met Lys Gln Leu Arg Val Ser		
195	200	205
Gln		
<210> SEQ ID NO 20		
<211> LENGTH: 489		
<212> TYPE: PRT		
<213> ORGANISM: Adenovirus type 36		
<400> SEQUENCE: 20		
Met Ala Gly Gly Ser Gln Asp Val Arg Arg Phe Met Glu Arg Glu Ala		
1	5	10
Thr Pro Pro Arg Gly His Gly Ser Ala Arg Tyr Pro Pro Glu Gln Glu		
20	25	30
Arg Ser Pro Ser Pro Pro Pro Pro Leu Pro Thr Lys Arg Arg Lys Tyr		
35	40	45
Gln Arg Val Gly Ser Gly Ser Ser Glu Glu Asp Val Val Pro Val Asp		
50	55	60
Ser Pro Pro Lys Lys Lys Gln Ala Arg Lys Thr Lys His Val Thr Lys		
65	70	75
Val Asp Pro Asp Glu Glu Met Pro Gln Glu Asp Ala Val Ile Val Gly		
85	90	95
Val Gly Phe Ser Gln Pro Pro Val Leu Leu Lys Glu Gly Lys Asp Gly		
100	105	110
Lys Arg Ile Val Glu Pro Ala Thr Pro Gly Val Leu Asn Val Arg Asn		
115	120	125
Pro Leu Ser Leu Pro Leu Val Ser Ser Trp Glu Lys Gly Met Asp Thr		
130	135	140
Met Asn Val Leu Met Glu Arg Tyr Arg Val Asp Ser Gly Leu Arg Asp		
145	150	155
Ala Tyr Lys Leu Met Pro Glu Gln Thr Glu Ile Phe Gln Lys Met Cys		
165	170	175
Gln Thr Trp Met Asn Glu Glu Ala Arg Gly Leu Gln Leu Thr Phe Thr		
180	185	190
Thr Gln Lys Ala Phe Ser Thr Val Met Gly Arg Leu Leu Gln Gly Tyr		
195	200	205
Ile Phe Ser His Ser Gly Ile Ala His Lys Asn Trp Glu Cys Thr Gly		
210	215	220
Cys Ala Leu Trp Asp His Gly Cys Thr Glu Val Glu Gly Gln Leu Lys		
225	230	235
Cys Leu His Gly Thr Val Met Ile His Lys Asp His Val Val Glu Met		
245	250	255
Asp Val Thr Ser Glu Asn Gly Gln Arg Ala Leu Lys Glu Gln Pro Ser		
260	265	270
Lys Ala Lys Val Thr Gln Asn Arg Trp Gly Arg Ser Val Val Gln Leu		
275	280	285
Thr Ser His Asp Ala Arg Cys Cys Val Gln Asp Ala Gly Cys Gly Asn		
290	295	300
Asn Gln Phe Ser Gly Lys Ser Cys Gly Leu Phe Phe Ser Glu Gly Ala		
305	310	315
Lys Ala Gln Gln Ala Phe Lys Gln Ile Ser Ala Phe Val Lys Ala Leu		
325	330	335
Tyr Pro Asn Met Gln Arg Gly Ala Gly Met Met Leu Met Pro Ile His		

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340	345	350
Cys Glu Cys Asn His Lys Pro Gln Ser Val Pro Phe Leu Gly Arg Gln		
355	360	365
Leu Cys Lys Met Thr Pro Phe Gly Leu Ser Asn Ala Glu Asp Leu Asp		
370	375	380
Lys Asp Gln Ile Thr Asp Lys Ser Val Leu Ala Ser Val Lys Tyr Pro		
385	390	395
Ser Leu Met Val Phe Gln Cys Cys Asn Pro Val Tyr Arg Asn Ser Arg		
405	410	415
Ala Gln Ser Thr Gly Pro Asn Cys Asp Phe Lys Ile Ser Ala Pro Asp		
420	425	430
Met Leu Gly Ala Leu Gln Met Ser Arg Arg Met Trp Ser Glu Thr Phe		
435	440	445
Pro Glu Ile Pro Val Pro Lys Leu Val Ile Pro Glu Phe Lys Trp Leu		
450	455	460
Pro Lys Tyr Gln Tyr Arg Asn Val Ala Leu Pro Ser Ala Ala His Asn		
465	470	475
Asp Glu Arg Glu Asn Pro Phe Asp Phe		
485		

<210> SEQ ID NO 21

<211> LENGTH: 731

<212> TYPE: PRT

<213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 21

Met Glu Glu Gln Pro Arg Lys Gln Glu Gln Glu Glu Asp Leu Thr Thr		
1	5	10
His Glu Gln Pro Lys Ile Glu Gln Asp Leu Gly Phe Glu Glu Pro Ala		
20	25	30
Arg Leu Glu Pro Pro Gln Asp Glu Gln Glu His Glu Gln Asp Ala Gly		
35	40	45
Gln Glu Glu Thr Asp Ala Gly Leu Glu His Gly Tyr Leu Gly Gly Glu		
50	55	60
Glu Asp Val Leu Leu Lys His Leu Gln Arg Gln Ser Leu Ile Leu Arg		
65	70	75
Asp Ala Leu Ala Asp Arg Ser Glu Thr Pro Leu Ser Val Glu Glu Leu		
85	90	95
Cys Arg Ala Tyr Glu Leu Asn Leu Phe Ser Pro Arg Val Pro Pro Lys		
100	105	110
Arg Gln Pro Asn Gly Thr Cys Glu Pro Asn Pro Arg Leu Asn Phe Tyr		
115	120	125
Pro Val Phe Ala Val Pro Glu Ala Leu Ala Thr Tyr His Ile Phe Phe		
130	135	140
Lys Asn Gln Lys Ile Pro Val Ser Cys Arg Ala Asn Arg Thr Arg Ala		
145	150	155
Asp Ala Leu Leu Ala Leu Gly Pro Gly Ala Arg Ile Pro Asp Ile Ala		
165	170	175
Ser Leu Glu Glu Val Pro Lys Ile Phe Glu Gly Leu Gly Arg Asp Glu		
180	185	190
Thr Arg Ala Ala Asn Ala Leu Lys Glu Thr Ala Glu Glu Glu Gly His		
195	200	205
Thr Ser Ala Leu Val Glu Leu Glu Gly Asp Asn Ala Arg Leu Val Val		
210	215	220

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Leu	Lys	Arg	Ser	Val	Glu	Leu	Thr	His	Phe	Ala	Tyr	Pro	Ala	Val	Asn	225	230	235	240
Leu	Pro	Pro	Lys	Val	Met	Arg	Arg	Ile	Met	Asp	Gln	Leu	Ile	Met	Pro	245	250	255	
His	Ile	Glu	Ala	Ile	Asp	Glu	Thr	Gln	Glu	Gln	Arg	Pro	Glu	Asp	Ala	260	265	270	
Arg	Pro	Val	Val	Ser	Asp	Glu	Met	Leu	Ala	Arg	Trp	Leu	Gly	Thr	Arg	275	280	285	
Asp	Pro	Gln	Ala	Leu	Glu	Gln	Arg	Arg	Lys	Leu	Met	Leu	Ala	Val	Val	290	295	300	
Leu	Val	Thr	Leu	Glu	Leu	Glu	Cys	Met	Arg	Arg	Phe	Phe	Cys	Asp	Pro	305	310	315	320
Glu	Thr	Leu	Arg	Lys	Val	Glu	Glu	Thr	Leu	His	Tyr	Thr	Phe	Arg	His	325	330	335	
Gly	Phe	Val	Arg	Gln	Ala	Cys	Lys	Ile	Ser	Asn	Val	Glu	Leu	Thr	Asn	340	345	350	
Leu	Val	Ser	Cys	Leu	Gly	Ile	Leu	His	Glu	Asn	Arg	Leu	Gly	Gln	Thr	355	360	365	
Val	Leu	His	Ser	Thr	Leu	Lys	Gly	Glu	Ala	Arg	Arg	Asp	Tyr	Val	Arg	370	375	380	
Asp	Cys	Val	Phe	Leu	Phe	Leu	Cys	His	Thr	Trp	Gln	Ala	Ala	Met	Gly	385	390	395	400
Val	Trp	Gln	Gln	Cys	Leu	Glu	Asp	Glu	Asn	Leu	Lys	Glu	Leu	Asp	Lys	405	410	415	
Leu	Leu	Ala	Arg	Asn	Leu	Lys	Lys	Leu	Trp	Thr	Gly	Phe	Asp	Glu	Arg	420	425	430	
Thr	Val	Ala	Ser	Asp	Leu	Ala	Glu	Ile	Val	Phe	Pro	Glu	Arg	Leu	Arg	435	440	445	
His	Thr	Leu	Lys	Gly	Gly	Leu	Pro	Asp	Phe	Met	Ser	Gln	Ser	Met	Leu	450	455	460	
Gln	Asn	Tyr	Arg	Thr	Phe	Ile	Leu	Glu	Arg	Ser	Gly	Ile	Leu	Pro	Ala	465	470	475	480
Thr	Cys	Asn	Ala	Phe	Pro	Ser	Asp	Phe	Val	Pro	Leu	Ser	Tyr	Arg	Glu	485	490	495	
Cys	Pro	Pro	Pro	Leu	Trp	Ser	His	Cys	Tyr	Leu	Leu	Gln	Leu	Ala	Asn	500	505	510	
Tyr	Ile	Ser	Tyr	His	Ser	Asp	Val	Ile	Glu	Asp	Val	Ser	Gly	Glu	Gly	515	520	525	
Leu	Leu	Glu	Cys	His	Cys	Arg	Cys	Asn	Leu	Cys	Ser	Pro	His	Arg	Ser	530	535	540	
Leu	Val	Cys	Asn	Pro	Gln	Leu	Leu	Ser	Glu	Thr	Gln	Val	Ile	Gly	Thr	545	550	555	560
Phe	Glu	Leu	Gln	Gly	Pro	Glu	Lys	Ser	Thr	Ala	Pro	Leu	Lys	Leu	Thr	565	570	575	
Pro	Gly	Leu	Trp	Thr	Ser	Ala	Tyr	Leu	Arg	Lys	Phe	Val	Pro	Glu	Asp	580	585	590	
Tyr	His	Ala	His	Glu	Ile	Lys	Phe	Phe	Glu	Asp	Gln	Ser	Arg	Pro	Gln	595	600	605	
His	Ala	Asp	Leu	Thr	Ala	Cys	Val	Ile	Thr	Gln	Gly	Ala	Ile	Leu	Ala	610	615	620	
Gln	Leu	His	Ala	Ile	Gln	Lys	Ser	Arg	Gln	Glu	Phe	Leu	Leu	Lys	Lys	625	630	635	640
Gly	Arg	Gly	Val	Tyr	Leu	Asp	Pro	Gln	Thr	Gly	Glu	Val	Leu	Asn	Pro				

645										650					655				
Gly	Leu	Pro	Gln 660	His	Ala	Glu	Glu	Glu 665	Ala	Gly	Ala	Ala	Ser 670	Gly	Gly				
Asp	Gly	Arg 675	Arg	Met	Gly	Gln	Pro 680	Gly	Arg	Gly	Gly	Arg 685	Met	Gly	Gly				
Gly	Asp 690	Arg	Gly	Gly	Arg	Ile 695	Gly	Arg	Gly	Gly	Arg 700	Gly	Ala	Gly	Asn				
Arg 705	Ala	Ala	Arg	Arg	Arg 710	Thr	Ile	Arg	Ala	Gly 715	Ser	Pro	Gly	Gly	His 720				
Gly	Tyr	Asn	Leu	Arg 725	Ser	Gly	Gln	Ala	Ser 730	Ser									

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<210> SEQ ID NO 22
<211> LENGTH: 172
<212> TYPE: PRT
<213> ORGANISM: Adenovirus type 36
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<400> SEQUENCE: 22

Met	Pro	Arg	Lys	Lys	Gln	Glu	Pro	Leu	Val	Glu	Glu	Met	Glu	Glu	Glu
1				5					10					15	
Trp	Asp	Ser	Gln	Ala	Glu	Glu	Asp	Glu	Trp	Glu	Glu	Glu	Thr	Glu	Glu
			20					25					30		
Glu	Glu	Leu	Glu	Glu	Val	Glu	Glu	Glu	Gln	Ala	Thr	Glu	Gln	Pro	Val
		35					40					45			
Ala	Ala	Pro	Ser	Ala	Pro	Ala	Ala	Pro	Ala	Val	Thr	Asp	Thr	Thr	Ser
	50					55					60				
Ala	Pro	Val	Lys	Pro	Pro	Arg	Arg	Trp	Asp	Arg	Val	Lys	Gly	Asp	Ala
65					70					75					80
Lys	Lys	Lys	Gln	Val	Arg	Gly	Val	Ala	Gly	Gly	Gly	Leu	Arg	Ile	Ala
			85						90					95	
Ala	Asn	Glu	Pro	Ser	Thr	Thr	Arg	Glu	Leu	Arg	Asn	Arg	Ile	Phe	Pro
			100					105					110		
Thr	Leu	Tyr	Ala	Ile	Phe	Gln	Gln	Ser	Arg	Gly	Gln	Gln	Gln	Glu	Leu
		115					120					125			
Lys	Val	Lys	Asn	Arg	Ser	Leu	Arg	Ser	Leu	Thr	Arg	Ser	Cys	Leu	Tyr
	130					135					140				
His	Lys	Asn	Glu	Asp	Gln	Leu	Gln	Arg	Thr	Leu	Glu	Asp	Ala	Glu	Ala
145					150					155					160
Leu	Phe	His	Lys	Tyr	Cys	Ala	Leu	Thr	Leu	Lys	Asp				
			165						170						

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<210> SEQ ID NO 23
<211> LENGTH: 136
<212> TYPE: PRT
<213> ORGANISM: Adenovirus type 36
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<400> SEQUENCE: 23

Met	Pro	Arg	Lys	Lys	Gln	Glu	Pro	Leu	Val	Glu	Glu	Met	Glu	Glu	Glu
1				5					10					15	
Trp	Asp	Ser	Gln	Ala	Glu	Glu	Asp	Glu	Trp	Glu	Glu	Glu	Thr	Glu	Glu
			20					25					30		
Glu	Glu	Leu	Glu	Glu	Val	Glu	Glu	Glu	Gln	Ala	Thr	Glu	Gln	Pro	Val
		35					40					45			
Ala	Ala	Pro	Ser	Ala	Pro	Ala	Ala	Pro	Ala	Val	Thr	Asp	Thr	Thr	Ser
	50					55					60				
Ala	Pro	Val	Lys	Pro	Pro	Arg	Arg	Trp	Asp	Arg	Val	Lys	Gly	Asp	Gly

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65	70	75	80
Lys His Glu Arg Gln Gly Tyr Arg Ser Trp Arg Ala His Lys Ala Ala			
	85	90	95
Ile Ile Ala Cys Leu Gln Asp Cys Gly Gly Asn Ile Ala Phe Ala Arg			
	100	105	110
Arg Tyr Leu Leu Phe His Arg Gly Val Asn Ile Pro Arg Asn Val Leu			
	115	120	125
His Tyr Tyr Arg His Leu His Ser			
	130	135	

<210> SEQ ID NO 24
 <211> LENGTH: 227
 <212> TYPE: PRT
 <213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 24

Met Ser Lys Glu Ile Pro Thr Pro Tyr Met Trp Ser Tyr Gln Pro Gln			
1	5	10	15
Met Gly Leu Ala Ala Gly Ala Ser Gln Asp Tyr Ser Thr Arg Met Asn			
	20	25	30
Trp Leu Ser Ala Gly Pro Ser Met Ile Ser Arg Val Asn Gly Val Arg			
	35	40	45
Asn His Arg Asn Gln Ile Leu Leu Glu Gln Ala Ala Val Thr Ser Thr			
	50	55	60
Pro Arg Ala Lys Leu Asn Pro Arg Asn Trp Pro Ser Thr Leu Val Tyr			
	65	70	75
Gln Glu Ile Pro Gly Pro Thr Thr Val Leu Leu Pro Arg Asp Ala Leu			
	85	90	95
Ala Glu Val Arg Met Thr Asn Ser Gly Val Gln Leu Ala Gly Gly Ala			
	100	105	110
Ser Arg Cys Pro Leu Arg Pro Gln Ser Gly Ile Lys Thr Leu Met Ile			
	115	120	125
Arg Gly Arg Gly Thr Gln Leu Asn Asp Glu Leu Val Ser Ser Ser Ile			
	130	135	140
Gly Leu Arg Pro Asp Gly Val Phe Gln Leu Ala Gly Ala Gly Arg Ser			
	145	150	155
Ser Phe Thr Pro Asn Gln Ala Tyr Leu Thr Leu Gln Ser Ser Ser Ser			
	165	170	175
Glu Pro Arg Ser Gly Gly Ile Gly Thr Leu Gln Phe Val Glu Glu Phe			
	180	185	190
Val Pro Ser Val Tyr Phe Asn Pro Phe Ser Gly Ser Pro Gly Leu Tyr			
	195	200	205
Pro Asp Glu Phe Ile Pro Asn Phe Asp Ala Val Arg Glu Ala Val Asp			
	210	215	220
Gly Tyr Asp			
225			

<210> SEQ ID NO 25
 <211> LENGTH: 106
 <212> TYPE: PRT
 <213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 25

Met Ser His Gly Asp Ser Ala Glu Leu Ala Arg Leu Arg His Leu Asp			
1	5	10	15
His Cys Arg Arg Leu Arg Cys Phe Ala Arg Glu Ser Cys Gly Leu Ile			


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      20      25      30
Tyr Phe Glu Leu Pro Glu Glu His Pro Asn Gly Pro Ala His Gly Val
   35           40           45

Arg Ile Thr Val Glu Gly Thr Ala Glu Ser His Leu Val Arg Phe Phe
   50           55           60

Thr Gln Gln Pro Phe Leu Val Glu Arg Asp Arg Gly Ala Thr Thr Tyr
   65           70           75           80

Thr Val Tyr Cys Ile Cys Pro Thr Pro Lys Leu His Glu Asn Phe Cys
   85           90           95

Cys Thr Leu Cys Gly Glu Phe Asn Lys Ser
   100          105

<210> SEQ ID NO 26
<211> LENGTH: 197
<212> TYPE: PRT
<213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 26

Met Arg Ile Phe Ala Val Leu Phe Val Val Ser Leu Ile Lys Ala Glu
 1           5           10           15

Leu Arg Thr Tyr Phe Gly Ile Pro Cys Arg His Gln Ile His Lys Thr
   20           25           30

Ile Asn Phe Thr Phe Glu Glu Gln Val Asn Phe Thr Cys Lys Pro His
   35           40           45

Lys Lys Tyr Val Thr Trp Phe Tyr Gln Asn Thr Thr Leu Ala Val Ala
   50           55           60

Asn Thr Cys Ser Asn Asp Gly Val Leu Leu Pro Asn Asn Leu Thr Ser
   65           70           75           80

Gly Leu Thr Phe Ser Val Lys Arg Ala Lys Leu Ile Leu His Arg Pro
   85           90           95

Ile Val Glu Gly Thr Tyr Gln Cys Gln Ser Gly Pro Cys Phe His Ser
  100          105          110

Phe Thr Leu Val Asn Val Thr Gly Ser Ser Thr Val Ala Pro Glu Thr
  115          120          125

Asn Leu Leu Ser Asp Thr Asn Thr Pro Lys Thr Gly Gly Glu Leu Trp
  130          135          140

Val Pro Ser Leu Thr Glu Gly Gly Ser His Ile Glu Ala Val Gly Tyr
  145          150          155          160

Leu Ile Leu Gly Val Val Leu Gly Gly Cys Ile Ala Val Leu Tyr Tyr
  165          170          175

Leu Pro Cys Trp Val Glu Ile Arg Val Phe Ile Cys Trp Val Arg His
  180          185          190

Cys Gly Glu Glu Pro
 195

<210> SEQ ID NO 27
<211> LENGTH: 156
<212> TYPE: PRT
<213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 27

Met Lys Gly Leu Leu Leu Ile Ile Leu Ser Leu Val Gly Gly Leu Leu
 1           5           10           15

Ala Cys His Glu Gln Pro Arg Cys Asn Ile Thr Thr Gly Asn Glu Arg
  20          25          30

Asn Asp Cys Ser Val Val Ile Lys Cys Glu His Gln Cys Pro Leu Asn

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35	40	45
Ile Thr Phe Lys Asn Lys Thr Met Gly Asn Val Trp Val Gly Phe Trp		
50	55	60
Gln Pro Gly Asp Glu Gln Asn Tyr Thr Val Thr Ile His Gly Ser Asp		
65	70	75
Gly Asn His Thr Phe Gly Phe Lys Phe Ile Phe Glu Val Met Cys Asp		
	85	90
Ile Thr Leu His Val Ala Arg Leu His Gly Leu Trp Pro Pro Thr Lys		
	100	105
Glu Asn Met Val Gly Phe Ser Leu Ala Phe Val Ile Met Ala Cys Ala		
	115	120
Met Ser Gly Leu Leu Val Gly Ala Leu Val Trp Phe Leu Lys Arg Lys		
	130	135
Pro Arg Tyr Gly Asn Glu Glu Lys Glu Lys Leu Leu		
145	150	155
<210> SEQ ID NO 28		
<211> LENGTH: 418		
<212> TYPE: PRT		
<213> ORGANISM: Adenovirus type 36		
<400> SEQUENCE: 28		
Met Asn Thr Leu Thr Ser Val Val Leu Leu Ser Leu Leu Val Ile Asn		
1	5	10
Val Glu Cys Ala Asp Pro Ile Leu Val Ser Val Asp Trp Gly Lys Asn		
	20	25
Leu Thr Leu Glu Gly Pro Lys Glu Thr Pro Val Glu Trp Trp Gly Gly		
	35	40
Arg Asn Ile Gln Gln Leu Cys Ile Gly Asn Gln Thr Lys His Lys Glu		
	50	55
Leu Ser His Arg Cys Asn Val Gln Asn Ile Thr Leu Leu Phe Val Asn		
	65	70
Thr Ser Phe Asn Gly Asp Tyr Phe Gly Phe Lys Asn Asp Asn Ser Gly		
	85	90
Met Lys His Tyr Lys Val Thr Val Ile Pro Pro Lys Pro Ser Thr Arg		
	100	105
Lys Pro Leu Ser Pro Pro His Tyr Val Asn Ala Thr Met Gly Gln Asn		
	115	120
Leu Thr Leu Val Gly Pro Ala Asn Ile Pro Val Thr Trp Leu Ser Glu		
	130	135
Tyr Gly Thr Leu Cys Glu Gly Lys Lys Ile Leu His Lys Glu Leu Asn		
	145	150
His Thr Cys Asn Glu Gln Asn Leu Thr Leu Leu Phe Val Asn Met Thr		
	165	170
His Asn Gly Pro Tyr Phe Gly Phe Asp Lys Tyr Asn Ile Asp Arg Glu		
	180	185
Gln Tyr Glu Val Ser Ile Ile Ser Leu Phe Lys Val Gly Ala Gly Gln		
	195	200
Lys Lys Ile Gly Lys Gly Gln Lys Lys Glu Glu Lys Thr Lys Pro Asn		
	210	215
Ser Ser Asp Leu Gly Gln Arg Gln Ser Arg Pro Lys Lys Lys Asp Ile		
	225	230
Val Glu Glu Val Gln Ile Lys Thr Gly Glu Asn Arg Thr Leu Val Gly		
	245	250
		255

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Pro Pro Gly Lys Val Asp Trp Ile Lys Leu Ser Ser Gly Asn Asn Asn
    260                265                270

Val Leu Lys Leu Cys Asn Gly Asp Lys Tyr Ile Lys His Thr Cys Asp
    275                280                285

Gly Gln Asn Leu Thr Leu Ile Asn Val Thr Arg Ile Tyr Asp Gly Thr
    290                295                300

Tyr Tyr Gly Ser Ser Asn Asp Gly Ser Ser His Tyr Lys Val Thr Ile
    305                310                315                320

Tyr Glu Leu His Lys Val Asn Lys Thr Lys Ser Met Leu Lys Pro Tyr
    325                330                335

Thr Thr Lys Arg Thr Thr Val Asn Ala Thr Asp Asp Ser Ala His Lys
    340                345                350

Ile Ala Leu Gln Gln Glu Asn Asn Gly Gln Thr Glu Asn Asp Gln Glu
    355                360                365

Ser Lys Ile Pro Ser Ala Thr Val Ala Ile Val Val Gly Val Ile Ala
    370                375                380

Gly Phe Ile Thr Ile Ile Ile Val Ile Leu Cys Tyr Ile Cys Cys Arg
    385                390                395                400

Lys Arg Pro Arg Ala Tyr Asn Asn Met Val Asp Pro Leu Leu Ser Phe
    405                410                415

Ser Tyr

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<210> SEQ ID NO 29
<211> LENGTH: 284
<212> TYPE: PRT
<213> ORGANISM: Adenovirus type 36

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<400> SEQUENCE: 29

Met Lys Ala Phe Thr Ala Cys Val Leu Ile Ser Ile Ile Thr Leu Ser
 1          5          10          15

Leu Ala Ala Pro Lys Pro Glu Val Tyr Thr Gln Val Asn Val Thr Arg
 20          25          30

Gly Gly Asn Ala Thr Leu Asp Gly Pro Phe Asn Asn Asn Thr Trp Thr
 35          40          45

Arg Tyr His Asp Asp Gly Arg Lys Asn Gly Trp Met Asn Ile Cys Lys
 50          55          60

Trp Ser Asp Pro Ser Tyr Thr Cys His Ser Asn Gly Ser Leu Ser Ile
 65          70          75          80

Phe Ala Phe Asn Ile Ser Ser Gly Lys Tyr Lys Val Gln Ser Tyr Thr
 85          90          95

Asn Ser Tyr Asn Gly Leu Asp Gly Tyr Glu Lys Leu Glu Val Lys Met
100          105          110

Phe Asn Leu Thr Val Ile Glu Pro Pro Thr Thr Arg Ala Pro Thr Thr
115          120          125

Val Arg Thr Thr Lys Glu Thr Thr Gln Pro Thr Thr Val Pro Thr Thr
130          135          140

His Pro Thr Thr Thr Val Ser Thr Thr Ile Glu Thr Thr Thr His Thr
145          150          155          160

Thr Gln Leu Asp Thr Thr Val Gln Asn Thr Thr Leu Leu Ile Glu Phe
165          170          175

Leu Leu Arg Gly Asn Glu Ser Thr Thr Asp Gln Thr Glu Ala Thr Ser
180          185          190

Ser Ala Phe Ser Ser Thr Ala Asn Leu Thr Ser Leu Ala Trp Thr Asn
195          200          205

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Glu Thr Gly Val Ser Leu Met His Gly Gln Pro Tyr Ser Gly Leu Asp
 210 215 220

Ile Gln Ile Thr Phe Leu Val Val Cys Gly Ile Phe Ile Leu Val Val
 225 230 235 240

Leu Leu Tyr Phe Val Cys Cys Lys Ala Arg Glu Lys Ser Ser Arg Pro
 245 250 255

Ile Tyr Arg Pro Val Ile Gly Glu Pro Gln Pro Leu Gln Val Glu Gly
 260 265 270

Gly Leu Arg Asn Leu Leu Phe Ser Phe Ser Val Trp
 275 280

<210> SEQ ID NO 30
 <211> LENGTH: 91
 <212> TYPE: PRT
 <213> ORGANISM: Adenovirus type 36
 <400> SEQUENCE: 30

Met Ile Pro Arg Phe Phe Leu Phe Asn Ile Leu Phe Cys Leu Phe Asn
 1 5 10 15

Ile Cys Ala Ala Phe Ala Ala Val Ser His Ala Ser Pro Asp Cys Leu
 20 25 30

Gly Pro Phe Pro Thr Tyr Leu Leu Phe Ala Leu Leu Thr Cys Thr Cys
 35 40 45

Val Cys Ser Ile Val Cys Leu Val Val Thr Phe Leu Gln Leu Ile Asp
 50 55 60

Trp Cys Cys Ala Arg Tyr Asn Tyr Leu His His Ser Pro Glu Tyr Arg
 65 70 75 80

Asp Lys Asn Val Ala Arg Ile Leu Arg Leu Ile
 85 90

<210> SEQ ID NO 31
 <211> LENGTH: 124
 <212> TYPE: PRT
 <213> ORGANISM: Adenovirus type 36
 <400> SEQUENCE: 31

Met Gln Thr Leu Leu Ile Leu Leu Ser Leu Leu Ser Pro Ala Leu Ala
 1 5 10 15

Asp Cys Lys Phe Ala Asp Ile Trp Asn Phe Leu Asp Cys Tyr Gln Glu
 20 25 30

Lys Met Asp Met Pro Ser Tyr Tyr Leu Val Ile Val Gly Val Val Met
 35 40 45

Val Cys Ser Cys Thr Phe Phe Ala Ile Met Ile Tyr Pro Cys Phe Asp
 50 55 60

Leu Gly Trp Asn Ser Val Glu Ala Phe Thr Tyr Thr Leu Glu Ser Ser
 65 70 75 80

Ser Leu Ala Ser Thr Pro Pro Pro Thr Pro Pro Pro Arg Arg Asn Gln
 85 90 95

Phe Pro Leu Ile Gln Tyr Leu Glu Glu Pro Pro Pro Arg Pro Pro Ser
 100 105 110

Thr Val Ser Tyr Phe His Ile Thr Gly Gly Asp Asp
 115 120

<210> SEQ ID NO 32
 <211> LENGTH: 130
 <212> TYPE: PRT
 <213> ORGANISM: Adenovirus type 36

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<400> SEQUENCE: 32

Met Thr Asp His His Leu Asp Leu Glu Met Asp Gly Gln Ala Ser Glu
 1 5 10 15
 Gln Arg Ile Leu Gln Leu Arg Val Arg Gln Gln Gln Glu Arg Ala Ala
 20 25 30
 Lys Glu Leu Leu Asp Ala Ile Asn Ile His Gln Cys Lys Lys Gly Ile
 35 40 45
 Phe Cys Leu Val Lys Gln Ala Lys Ile Thr Tyr Glu Leu Val Ser Asn
 50 55 60
 Gly Lys Gln His Arg Leu Thr Tyr Glu Met Pro Gln Gln Lys Gln Lys
 65 70 75 80
 Phe Thr Cys Met Val Gly Val Asn Pro Ile Val Ile Thr Gln Gln Ser
 85 90 95
 Gly Glu Thr Ser Gly Cys Ile His Cys Ser Cys Glu Ser Pro Glu Cys
 100 105 110
 Ile Tyr Ser Leu Leu Lys Thr Leu Cys Gly Leu Arg Asp Leu Leu Pro
 115 120 125
 Met Asn
 130

<210> SEQ ID NO 33

<211> LENGTH: 49

<212> TYPE: PRT

<213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 33

Met Lys Ile Val Asp Gln Glu Phe Asp Ile Pro Phe Lys Val Trp Arg
 1 5 10 15
 Lys Phe Ala Ala Arg Arg Gly Leu Glu Tyr Gln Ser Trp Glu Glu Gly
 20 25 30
 Thr Glu Val Leu Leu Asn Asn Tyr Thr Arg Asp Ile Leu Ser Asp Phe
 35 40 45
 Lys

<210> SEQ ID NO 34

<211> LENGTH: 371

<212> TYPE: PRT

<213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 34

Met Ser Lys Arg Leu Arg Val Glu Asp Asp Phe Asn Pro Val Tyr Pro
 1 5 10 15
 Tyr Gly Tyr Ala Arg Asn Gln Asn Ile Pro Phe Leu Thr Pro Pro Phe
 20 25 30
 Val Ser Ser Asp Gly Phe Gln Asn Phe Pro Pro Gly Val Leu Ser Leu
 35 40 45
 Lys Leu Ala Asp Pro Ile Ala Ile Ala Asn Gly Asn Val Ser Leu Lys
 50 55 60
 Val Gly Gly Gly Leu Thr Val Glu Gln Gln Ser Gly Lys Leu Ser Val
 65 70 75 80
 Asp Thr Lys Ala Pro Leu Gln Val Ala Asn Asp Asn Lys Leu Glu Leu
 85 90 95
 Ser Tyr Asp Asp Pro Phe Lys Val Glu Asn Asn Lys Leu Gly Ile Lys
 100 105 110
 Ala Gly His Gly Leu Ala Val Val Thr Lys Glu Asn Thr Ser Leu Pro
 115 120 125

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Ser Leu Val Gly Thr Leu Val Val Leu Thr Gly Lys Gly Ile Gly Thr
 130 135 140
 Gly Ser Ser Ala His Gly Gly Thr Ile Asp Val Arg Leu Gly Glu Gly
 145 150 155 160
 Gly Gly Leu Ser Phe Asp Glu Lys Gly Asp Leu Val Ala Trp Asp Lys
 165 170 175
 Lys Asn Asp Thr Arg Thr Leu Trp Thr Thr Pro Asp Pro Ser Pro Asn
 180 185 190
 Cys Lys Val Glu Thr Ala Arg Asp Ser Lys Leu Thr Leu Ala Leu Thr
 195 200 205
 Lys Cys Gly Ser Gln Ile Leu Ala Thr Val Ser Leu Leu Val Val Thr
 210 215 220
 Gly Lys Tyr Ala Ile Ile Ser Asp Thr Val Asn Pro Lys Gln Phe Ser
 225 230 235 240
 Ile Lys Leu Leu Phe Asn Asp Lys Gly Val Leu Leu Ser Asp Ser Asn
 245 250 255
 Leu Asp Gly Thr Tyr Trp Asn Tyr Arg Ser Asn Asn Asn Ile Gly
 260 265 270
 Thr Pro Tyr Lys Glu Ala Val Gly Phe Met Pro Ser Thr Thr Ala Tyr
 275 280 285
 Pro Lys Pro Thr Asn Asn Thr Ser Thr Asp Pro Asp Lys Lys Val Ser
 290 295 300
 Gln Gly Lys Asn Lys Ile Val Ser Asn Ile Tyr Leu Gly Gly Glu Val
 305 310 315 320
 Tyr Gln Pro Gly Phe Ile Val Val Lys Phe Asn Gln Glu Thr Asp Ala
 325 330 335
 Asn Cys Ala Tyr Ser Ile Thr Phe Asp Phe Gly Trp Gly Lys Val Tyr
 340 345 350
 Lys Asp Pro Ile Pro Tyr Asp Thr Ser Ser Phe Thr Phe Ser Tyr Ile
 355 360 365
 Ala Gln Glu
 370

<210> SEQ ID NO 35

<211> LENGTH: 130

<212> TYPE: PRT

<213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 35

Met Ser Thr Glu Glu Gln Ser Thr Ser Leu Arg His His Pro Tyr Arg
 1 5 10 15
 Arg Ala Arg Leu Pro Arg Ser Glu Glu Glu Thr Arg Ala Ser Leu Thr
 20 25 30
 Glu Gln His Pro Leu Leu Pro Asp Cys Asp His Ala Glu Tyr His Asn
 35 40 45
 Thr Val Thr Leu Asp Cys Glu Ala Arg Leu Glu Asp Phe Ser Glu Asp
 50 55 60
 Gly Phe Ile Ser Ile Thr Asp Pro Arg Leu Ala Arg Gln Glu Thr Val
 65 70 75 80
 Trp Ile Ile Asp Thr Lys Ser Ser Ser Arg Thr Asn Gln Asn Ile Pro
 85 90 95
 Leu Phe Lys Ala Thr Arg Ala Glu Arg Ile Val Tyr Thr Val Lys Trp
 100 105 110
 Ala Gly Gly Gly Arg Leu Thr Thr Arg Ala Gly Val Lys Ile Asn Lys

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115	120	125
Asp Thr		
130		
<210> SEQ ID NO 36 <211> LENGTH: 292 <212> TYPE: PRT <213> ORGANISM: Adenovirus type 36 <400> SEQUENCE: 36		
Met Ser Thr Glu Glu Gln Ser Thr Ser Leu Arg His His Pro Tyr Arg		
1 5 10 15		
Arg Ala Arg Leu Pro Arg Ser Glu Glu Glu Thr Arg Ala Ser Leu Thr		
20 25 30		
Glu Gln His Pro Leu Leu Pro Asp Cys Asp His Ala Glu Tyr His Asn		
35 40 45		
Val Ser Ser Val Arg Gly Leu Pro Cys Ala Ala Gly Phe Thr Leu Leu		
50 55 60		
Gln Glu Phe Pro Val Pro Trp Asp Met Ile Leu Thr Pro Glu Glu Ile		
65 70 75 80		
Lys Ile Leu Lys Arg Cys Met Ser Val Cys Leu Cys Pro Ala Thr Leu		
85 90 95		
Asp Leu Val Arg Ala Gln Met Val Ser Gly Tyr Glu Arg Trp Ile Leu		
100 105 110		
His Cys His Cys Ser Ser Pro Gly Ser Leu Gln Cys Arg Ala Gly Gly		
115 120 125		
Thr Leu Leu Ala Val Trp Phe Arg Arg Val Ile Tyr Gly Cys Met Phe		
130 135 140		
Asn Gln Arg Phe Pro Trp Tyr Arg Gln Ile Val Asn Arg Asn Met Pro		
145 150 155 160		
Lys Glu Ile Met Tyr Met Gly Ser Val Phe Met Arg Gly Arg His Leu		
165 170 175		
Ile Tyr Cys Arg Ile Trp Tyr Asp Gly His Val Gly Ser Ile Ile Pro		
180 185 190		
Asn Met Ser Phe Gly Trp Ser Thr Leu Asn Tyr Gly Leu Leu Asn Asn		
195 200 205		
Met Val Ile Met Cys Cys Thr Tyr Cys Glu Asn Met Ser Glu Ile Arg		
210 215 220		
Met Arg Cys Cys Ala Arg Arg Thr Arg Arg Leu Met Leu Lys Ala Val		
225 230 235 240		
Gly Ile Ile Val Arg Glu Thr Cys Asp Pro Asp Pro Ile Cys Ser Ser		
245 250 255		
Arg Thr Glu Pro Arg Arg Gln Arg Leu Leu Arg Ala Leu Met Glu Arg		
260 265 270		
His Arg Pro Ile Leu Phe Ser Glu Tyr Glu Ser Val Arg Ser Ser His		
275 280 285		
Ser Thr Arg Leu		
290		
<210> SEQ ID NO 37 <211> LENGTH: 127 <212> TYPE: PRT <213> ORGANISM: Adenovirus type 36 <400> SEQUENCE: 37		
Met Cys Cys Trp Leu Tyr Pro Ala Pro Arg Val Ser Ser Pro Leu Gly		

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1	5	10	15
Tyr Asp Pro Asp Pro Arg Gly Asn Lys Asn Phe Lys Lys Met Tyr Val	20	25	30
Ser Val Pro Val Pro Arg Tyr Pro Gly Leu Gly Glu Ser Ser Asp Gly	35	40	45
Glu Arg Val Arg Ala Leu Asp Pro Ala Leu Pro Leu Phe Val Pro Gly	50	55	60
Leu Pro Ala Val Pro Gly Gly Arg His Pro Ala Gly Arg Val Val Gln	65	70	75
Glu Ser His Leu Arg Val His Val Gln Pro Ala Leu Pro Leu Val Pro	85	90	95
Pro Asp Cys Glu Gln Lys His Ala Gln Arg Asp His Val Tyr Gly Gln	100	105	110
Cys Val His Glu Gly Gln Ala Pro Asp Ile Leu Pro His Leu Val	115	120	125

<210> SEQ ID NO 38

<211> LENGTH: 120

<212> TYPE: PRT

<213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 38

Met Val Leu Pro Ile Leu Pro Pro Pro Pro Leu Asn Asp Arg Gln Gly	1	5	10	15
Ser Ile Asn Trp Met Gly Met Ala Tyr Arg Val Leu Ala Asp Val Met	20	25	30	
Arg Gly Ile Arg Met Asp Gly Leu Phe Val Ser Ser Asp Ala Glu Glu	35	40	45	
Leu Leu Gln Asn Leu Arg Glu Trp Met Tyr Phe Ser Trp Met Thr Glu	50	55	60	
Arg Gln Gln Arg Lys Asp Gly Arg Arg Arg Gly Ile Cys Cys Ser Arg	65	70	75	80
Ala Thr Phe Cys Trp Gln Lys Tyr Asp Lys Val Arg Lys Arg Val His	85	90	95	
Tyr Asn Glu His Arg Gly Thr Ile Asp Leu Ala Pro Pro Ser Ser Ile	100	105	110	
Pro Gln Gly Pro Phe Thr Thr Ile	115	120		

<210> SEQ ID NO 39

<211> LENGTH: 117

<212> TYPE: PRT

<213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 39

Met Lys Val Cys Leu Leu Met Lys Val Glu Gly Ala Leu Trp Glu Leu	1	5	10	15
Phe Asn Met Cys Gly Val Asp Leu His Gln Gln Phe Val Ala Ile Ile	20	25	30	
Gln Gly Trp Lys Asn Glu Asn Tyr Leu Gly Met Val Gln Asp Cys Asn	35	40	45	
Met Met Ile Glu Glu Gln Asp Gly Gly Pro Ala Phe Asn Val Leu Leu	50	55	60	
Phe Leu Asp Val Arg Val Glu Pro Leu Leu Glu Ala Thr Val Glu His	65	70	75	80
Leu Glu Asn Arg Ile Ile Phe Asp Leu Ala Val Cys Phe His Gln Asn				

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85	90	95
Ser Gly Gly Glu Arg Cys His Leu Arg Asp Leu Asn Phe Ile Leu Leu		
100	105	110
Arg Asp Arg Leu Glu		
115		

<210> SEQ ID NO 40
 <211> LENGTH: 130
 <212> TYPE: PRT
 <213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 40

Met	Leu	Glu	Arg	Arg	Gly	Val	Ser	Tyr	His	Ile	Val	Val	Pro	Gly	Ala
1			5						10					15	
Leu	Val	Thr	Tyr	Leu	Glu	Asp	Phe	Ser	Ile	Thr	Ala	Met	Ile	Lys	Glu
		20						25					30		
His	Leu	Pro	Arg	Phe	Ile	Thr	His	Leu	Leu	Glu	Gly	Ile	Thr	Gly	Asp
		35					40					45			
Thr	Lys	Arg	Ala	Tyr	Ser	Ser	Met	Gln	Phe	Leu	Gly	Ala	Asn	Tyr	Gly
	50					55					60				
Ala	Leu	Arg	Tyr	Ser	Leu	Thr	Leu	Ala	Ser	Pro	Thr	Leu	Ser	Pro	Gly
65					70					75				80	
Ser	Asp	Leu	Ala	Ser	Val	Val	Ala	Glu	Asp	Leu	Ser	Asp	Phe	Leu	Gln
			85						90					95	
Leu	Thr	Leu	Arg	Arg	Glu	Leu	Arg	Ala	Glu	Gly	Arg	Asn	Ser	Leu	Asn
			100					105					110		
Leu	Val	Val	Leu	Asn	Thr	Leu	Gln	Val	Val	Glu	Gln	Pro	Asp	Leu	Leu
		115				120						125			
Leu	Leu														
	130														

<210> SEQ ID NO 41
 <211> LENGTH: 125
 <212> TYPE: PRT
 <213> ORGANISM: Adenovirus type 36

<400> SEQUENCE: 41

Met	Ala	Glu	Ser	Leu	Tyr	Ala	Phe	Ile	Asp	Ser	Pro	Gly	Gly	Ile	Ala
1				5					10					15	
Pro	Val	Gln	Glu	Gly	Ala	Ser	Asn	Arg	Tyr	Ile	Phe	Phe	Cys	Pro	Glu
		20						25					30		
Ser	Phe	His	Ile	Pro	Pro	His	Gly	Val	Ile	Leu	Leu	His	Leu	Arg	Val
		35					40					45			
Ser	Val	Leu	Val	Pro	Thr	Gly	Tyr	Gln	Gly	Arg	Phe	Met	Ala	Leu	Asn
	50					55					60				
Asp	Tyr	His	Ala	Arg	Gly	Ile	Leu	Thr	Gln	Ser	Asp	Val	Ile	Phe	Ala
65					70					75				80	
Gly	Arg	Arg	His	Asp	Leu	Ser	Val	Leu	Leu	Phe	Asn	His	Thr	Asp	Arg
			85					90					95		
Phe	Leu	Tyr	Val	Arg	Glu	Gly	His	Pro	Val	Gly	Thr	Leu	Leu	Leu	Glu
			100					105					110		
Arg	Val	Ile	Phe	Pro	Ser	Val	Arg	Ile	Ala	Thr	Leu	Val			
		115				120					125				

<210> SEQ ID NO 42
 <211> LENGTH: 230
 <212> TYPE: PRT

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<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 42

Met Ala Asp Glu Ala Pro Val Glu Gln Gln Ser Gly Lys Leu Ser Val
1           5           10           15
Asp Thr Lys Ala Pro Leu Gln Val Ala Asn Asp Asn Lys Leu Glu Leu
20           25           30
Ser Tyr Asp Asp Pro Phe Lys Val Glu Asn Asn Lys Leu Gly Ile Lys
35           40           45
Ala Gly His Gly Leu Ala Val Val Thr Lys Glu Asn Thr Ser Leu Pro
50           55           60
Ser Leu Val Gly Thr Leu Val Val Gly Ser Ser Ala His Gly Gly Thr
65           70           75           80
Ile Asp Val Arg Leu Gly Glu Gly Gly Gly Leu Ser Phe Asp Glu Lys
85           90           95
Gly Thr Val Ser Leu Leu Val Val Thr Gly Lys Tyr Ala Ile Ile Ser
100          105          110
Asp Thr Val Asn Pro Lys Gln Phe Ser Ile Lys Leu Leu Phe Asn Asp
115          120          125
Lys Gly Val Leu Leu Ser Asp Ser Asn Leu Asp Gly Thr Tyr Trp Asn
130          135          140
Tyr Arg Ser Asn Asn Asn Asn Ile Gly Thr Pro Tyr Lys Glu Ala Val
145          150          155          160
Gly Phe Met Pro Ser Thr Thr Ala Tyr Pro Lys Pro Thr Asn Asn Thr
165          170          175
Ser Thr Asp Pro Asp Lys Lys Val Ser Gln Gly Lys Asn Lys Ile Val
180          185          190
Ser Asn Thr Asp Ala Asn Cys Ala Tyr Ser Ile Thr Phe Asp Phe Gly
195          200          205
Trp Gly Lys Val Tyr Lys Asp Pro Ile Pro Tyr Asp Thr Ser Ser Phe
210          215          220

His His His His His His
225          230

<210> SEQ ID NO 43
<211> LENGTH: 200
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 43

Met Ala Asp Glu Ala Pro Thr Asp Lys Glu Arg Gln Asn Gly Gly Gln
1           5           10           15
Pro Pro Thr Thr Lys Asp Val Thr Lys Thr Phe Gly Val Ala Ala Arg
20           25           30
Gly Gly Leu His Ile Thr Asp Lys Gly Leu Gln Ile Gly Glu Asp Glu
35           40           45
Asn Asn Glu Asp Gly Glu Glu Glu Ile Tyr Ala Asp Lys Thr Phe Gln
50           55           60
Pro Glu Pro Gln Val Gly Glu Glu Asn Trp Gln Asp Thr Asp Val Phe
65           70           75           80
Tyr Gly Gly Arg Ala Leu Lys Lys Glu Glu Lys Gly Gly Gln Ala Lys
85           90           95

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Phe	Leu	Asn	Gly	Glu	Asn	Gly	Gln	Pro	Ser	Lys	Asp	Gln	Asp	Ile	Thr
		100						105					110		
Leu	Ala	Phe	Phe	Asp	Leu	Lys	Gln	Asn	Asp	Thr	Gly	Thr	Thr	Gln	Asn
		115					120					125			
Gln	Pro	Asp	Val	Val	Met	Tyr	Thr	Glu	Asn	Val	Tyr	Leu	Gly	Lys	Glu
		130				135					140				
Asp	Thr	Ser	Ser	Ala	Ala	Asn	Leu	Thr	Asp	Gly	Ser	Gly	Ser	Asn	Thr
	145				150					155					160
Ala	Tyr	Gln	Gly	Val	Lys	Tyr	Glu	Asn	Gly	Ala	Gly	Asn	Gly	Ser	Trp
				165					170					175	
Lys	Val	Asp	Gly	Glu	Val	Ala	Ser	Gln	Asn	Gln	Ile	Ala	Lys	Gly	Asn
		180						185					190		
Leu	Tyr	His	His	His	His	His	His								
		195					200								

<210> SEQ ID NO 44
 <211> LENGTH: 955
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 44

Met	Ala	Asp	Glu	Ala	Pro	Ala	Thr	Pro	Ser	Met	Met	Pro	Gln	Trp	Ala
1				5					10					15	
Tyr	Met	His	Ile	Ala	Gly	Gln	Asp	Ala	Ser	Glu	Tyr	Leu	Ser	Pro	Gly
			20					25					30		
Leu	Val	Gln	Phe	Ala	Arg	Ala	Thr	Asp	Thr	Tyr	Phe	Ser	Leu	Gly	Asn
		35				40						45			
Lys	Phe	Arg	Asn	Pro	Thr	Val	Ala	Pro	Thr	His	Asp	Val	Thr	Thr	Asp
	50					55					60				
Arg	Ser	Gln	Arg	Leu	Thr	Leu	Arg	Phe	Val	Pro	Val	Asp	Arg	Glu	Asp
	65				70				75					80	
Thr	Thr	Tyr	Ser	Tyr	Lys	Ala	Arg	Phe	Thr	Leu	Ala	Val	Gly	Asp	Asn
			85					90						95	
Arg	Val	Leu	Asp	Met	Ala	Ser	Thr	Tyr	Phe	Asp	Ile	Arg	Gly	Val	Leu
		100						105					110		
Asp	Arg	Gly	Pro	Ser	Phe	Lys	Pro	Tyr	Ser	Gly	Thr	Ala	Tyr	Asn	Ser
		115				120						125			
Leu	Ala	Pro	Lys	Gly	Ala	Pro	Asn	Ser	Ser	Gln	Trp	Thr	Asp	Lys	Glu
	130					135					140				
Arg	Gln	Asn	Gly	Gly	Gln	Pro	Pro	Thr	Thr	Lys	Asp	Val	Thr	Lys	Thr
	145				150					155				160	
Phe	Gly	Val	Ala	Ala	Arg	Gly	Gly	Leu	His	Ile	Thr	Asp	Lys	Gly	Leu
			165					170						175	
Gln	Ile	Gly	Glu	Asp	Glu	Asn	Asn	Glu	Asp	Gly	Glu	Glu	Glu	Ile	Tyr
		180						185					190		
Ala	Asp	Lys	Thr	Phe	Gln	Pro	Glu	Pro	Gln	Val	Gly	Glu	Glu	Asn	Trp
		195				200						205			
Gln	Asp	Thr	Asp	Val	Phe	Tyr	Gly	Gly	Arg	Ala	Leu	Lys	Lys	Glu	Thr
	210					215					220				
Lys	Met	Lys	Pro	Cys	Tyr	Gly	Ser	Phe	Ala	Arg	Pro	Thr	Asn	Glu	Lys
	225				230					235				240	
Gly	Gly	Gln	Ala	Lys	Phe	Leu	Asn	Gly	Glu	Asn	Gly	Gln	Pro	Ser	Lys
			245					250					255		

Asp 305	Gln 260	Asp 275	Ile 290	Thr 305	Leu 310	Ala 325	Phe 340	Phe 355	Asp 370	Leu 385	Lys 400	Gln 415	Asn 430	Asp 445	Thr 460
Gly 305	Thr 275	Thr 290	Gln 305	Asn 310	Gln 325	Pro 340	Asp 355	Val 370	Val 385	Met 400	Tyr 415	Thr 430	Glu 445	Asn 460	Val 475
Tyr 305	Leu 290	Glu 305	Thr 310	Pro 325	Asp 340	Thr 355	His 370	Val 385	Val 400	Tyr 415	Lys 430	Pro 445	Gly 460	Lys 475	Glu 490
Asp 305	Thr 275	Ser 290	Ser 305	Ala 310	Ala 325	Asn 340	Leu 355	Thr 370	Gln 385	Gln 400	Ser 415	Met 430	Pro 445	Asn 460	Arg 475
Pro 305	Asn 260	Tyr 275	Ile 290	Gly 305	Phe 310	Arg 325	Asp 340	Asn 355	Phe 370	Val 385	Gly 400	Leu 415	Met 430	Tyr 445	Tyr 460
Asn 305	Ser 260	Thr 275	Gly 290	Asn 305	Met 310	Gly 325	Val 340	Leu 355	Ala 370	Gly 385	Gln 400	Ala 415	Ser 430	Gln 445	Leu 460
Asn 305	Ala 260	Val 275	Val 290	Asp 305	Leu 310	Gln 325	Asp 340	Arg 355	Asn 370	Thr 385	Glu 400	Leu 415	Ser 430	Tyr 445	Gln 460
Leu 305	Leu 290	Leu 305	Asp 310	Ser 325	Leu 340	Gly 355	Asp 370	Arg 385	Thr 400	Arg 415	Tyr 430	Phe 445	Ser 460	Met 475	Trp 490
Asn 385	Ser 370	Ala 385	Val 390	Asp 405	Ser 420	Tyr 435	Asp 450	Pro 465	Asp 480	Val 495	Arg 510	Ile 525	Ile 540	Glu 555	Asn 570
His 385	Gly 370	Val 385	Glu 390	Asp 405	Glu 420	Leu 435	Pro 450	Asn 465	Tyr 480	Cys 495	Phe 510	Pro 525	Leu 540	Asp 555	Gly 570
Ser 385	Gly 370	Ser 385	Asn 390	Thr 405	Ala 420	Tyr 435	Gln 450	Gly 465	Val 480	Lys 495	Tyr 510	Glu 525	Asn 540	Gly 555	Ala 570
Gly 385	Asn 370	Gly 385	Ser 390	Trp 405	Lys 420	Val 435	Asp 450	Gly 465	Glu 480	Val 495	Ala 510	Ser 525	Gln 540	Asn 555	Gln 570
Ile 385	Ala 370	Lys 385	Gly 390	Asn 405	Leu 420	Tyr 435	Ala 450	Met 465	Glu 480	Ile 495	Asn 510	Leu 525	Gln 540	Ala 555	Asn 570
Leu 465	Trp 450	Lys 465	Ser 470	Phe 485	Leu 500	Tyr 515	Ser 530	Asn 545	Val 560	Ala 575	Leu 590	Tyr 605	Leu 620	Pro 635	Asp 650
Ser 465	Tyr 450	Lys 465	Tyr 470	Thr 485	Pro 500	Ala 515	Asn 530	Ile 545	Thr 560	Leu 575	Pro 590	Thr 605	Asn 620	Thr 635	Asn 650
Thr 465	Tyr 450	Glu 465	Tyr 470	Met 485	Asn 500	Gly 515	Arg 530	Val 545	Val 560	Ala 575	Pro 590	Ser 605	Leu 620	Val 635	Asp 650
Ala 465	Tyr 450	Val 465	Asn 470	Ile 485	Gly 500	Ala 515	Arg 530	Trp 545	Ser 560	Leu 575	Asp 590	Pro 605	Met 620	Asp 635	Asn 650
Val 465	Asn 450	Pro 465	Phe 470	Asn 485	His 500	His 515	Arg 530	Asn 545	Ala 560	Gly 575	Leu 590	Arg 605	Tyr 620	Arg 635	Ser 650
Met 545	Leu 530	Leu 545	Gly 550	Asn 565	Gly 580	Arg 595	Tyr 610	Val 625	Pro 640	Phe 655	His 670	Ile 685	Gln 700	Val 715	Pro 730
Gln 545	Lys 530	Phe 545	Phe 550	Ala 565	Ile 580	Lys 595	Asn 610	Leu 625	Leu 640	Leu 655	Leu 670	Pro 685	Gly 700	Ser 715	Tyr 730
Thr 545	Tyr 530	Glu 545	Trp 550	Asn 565	Phe 580	Arg 595	Lys 610	Asp 625	Val 640	Asn 655	Met 670	Ile 685	Leu 700	Gln 715	Ser 730
Ser 545	Leu 530	Gly 545	Asn 550	Asp 565	Leu 580	Arg 595	Val 610	Asp 625	Gly 640	Ala 655	Ser 670	Val 685	Arg 700	Phe 715	Asp 730
Ser 545															

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675					680					685					
Gly	Ser	Gly	Phe	Asp	Pro	Tyr	Phe	Val	Tyr	Ser	Gly	Ser	Ile	Pro	Tyr
690						695					700				
Leu	Asp	Gly	Thr	Phe	Tyr	Leu	Asn	His	Thr	Phe	Lys	Lys	Val	Ser	Ile
705					710					715					720
Met	Phe	Asp	Ser	Ser	Val	Ser	Trp	Pro	Gly	Asn	Asp	Arg	Leu	Leu	Thr
				725					730					735	
Pro	Asn	Glu	Phe	Glu	Ile	Lys	Arg	Ser	Val	Asp	Gly	Glu	Gly	Tyr	Asn
			740					745				750			
Val	Ala	Gln	Cys	Asn	Met	Thr	Lys	Asp	Trp	Phe	Leu	Val	Gln	Met	Leu
			755					760				765			
Ser	His	Tyr	Asn	Ile	Gly	Tyr	Gln	Gly	Phe	Tyr	Val	Pro	Glu	Gly	Tyr
	770				775						780				
Lys	Asp	Arg	Met	Tyr	Ser	Phe	Phe	Arg	Asn	Phe	Gln	Pro	Met	Ser	Arg
785					790					795					800
Gln	Val	Val	Asp	Glu	Ile	Asn	Tyr	Lys	Asp	Tyr	Lys	Ala	Val	Thr	Leu
				805					810					815	
Pro	Phe	Gln	His	Asn	Asn	Ser	Gly	Phe	Thr	Gly	Tyr	Leu	Ala	Pro	Thr
			820					825					830		
Met	Arg	Gln	Gly	Gln	Pro	Tyr	Pro	Ala	Asn	Phe	Pro	Tyr	Pro	Leu	Ile
	835						840					845			
Gly	Gln	Thr	Ala	Val	Pro	Ser	Val	Thr	Gln	Lys	Lys	Phe	Leu	Cys	Asp
850						855					860				
Arg	Val	Met	Trp	Arg	Ile	Pro	Phe	Ser	Ser	Asn	Phe	Met	Ser	Met	Gly
865					870					875					880
Ala	Leu	Thr	Asp	Leu	Gly	Gln	Asn	Met	Leu	Tyr	Ala	Asn	Ser	Ala	His
				885					890					895	
Ala	Leu	Asp	Met	Thr	Phe	Glu	Val	Asp	Pro	Met	Asp	Glu	Pro	Thr	Leu
			900					905					910		
Leu	Tyr	Leu	Leu	Phe	Glu	Val	Phe	Asp	Val	Val	Arg	Val	His	Gln	Pro
	915						920					925			
His	Arg	Gly	Val	Ile	Glu	Ala	Val	Tyr	Leu	Arg	Thr	Pro	Phe	Ser	Ala
	930					935					940				
Gly	Asn	Ala	Thr	Thr	His	His	His	His	His	His					
945					950					955					

<210> SEQ ID NO 45

<211> LENGTH: 418

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 45

Met	Ala	Asp	Glu	Ala	Pro	Val	Glu	Gln	Gln	Ser	Gly	Lys	Leu	Ser	Val
1				5						10				15	
Asp	Thr	Lys	Ala	Pro	Leu	Gln	Val	Ala	Asn	Asp	Asn	Lys	Leu	Glu	Leu
			20					25					30		
Ser	Tyr	Asp	Asp	Pro	Phe	Lys	Val	Glu	Asn	Asn	Lys	Leu	Gly	Ile	Lys
		35					40					45			
Ala	Gly	His	Gly	Leu	Ala	Val	Val	Thr	Lys	Glu	Asn	Thr	Ser	Leu	Pro
	50					55					60				
Ser	Leu	Val	Gly	Thr	Leu	Val	Val	Gly	Ser	Ser	Ala	His	Gly	Gly	Thr
65					70					75				80	
Ile	Asp	Val	Arg	Leu	Gly	Glu	Gly	Gly	Gly	Leu	Ser	Phe	Asp	Glu	Lys

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85					90					95					
Gly	Thr	Val	Ser	Leu	Leu	Val	Val	Thr	Gly	Lys	Tyr	Ala	Ile	Ile	Ser
			100					105					110		
Asp	Thr	Val	Asn	Pro	Lys	Gln	Phe	Ser	Ile	Lys	Leu	Leu	Phe	Asn	Asp
			115				120						125		
Lys	Gly	Val	Leu	Leu	Ser	Asp	Ser	Asn	Leu	Asp	Gly	Thr	Tyr	Trp	Asn
			130				135						140		
Tyr	Arg	Ser	Asn	Asn	Asn	Asn	Ile	Gly	Thr	Pro	Tyr	Lys	Glu	Ala	Val
							150						155		160
Gly	Phe	Met	Pro	Ser	Thr	Thr	Ala	Tyr	Pro	Lys	Pro	Thr	Asn	Asn	Thr
													165		175
Ser	Thr	Asp	Pro	Asp	Lys	Lys	Val	Ser	Gln	Gly	Lys	Asn	Lys	Ile	Val
													180		190
Ser	Asn	Thr	Asp	Ala	Asn	Cys	Ala	Tyr	Ser	Ile	Thr	Phe	Asp	Phe	Gly
													195		205
Trp	Gly	Lys	Val	Tyr	Lys	Asp	Pro	Ile	Pro	Tyr	Asp	Thr	Ser	Ser	Phe
													210		220
Thr	Asp	Lys	Glu	Arg	Gln	Asn	Gly	Gly	Gln	Pro	Pro	Thr	Thr	Lys	Asp
													225		240
Val	Thr	Lys	Thr	Phe	Gly	Val	Ala	Ala	Arg	Gly	Gly	Leu	His	Ile	Thr
													230		255
Asp	Lys	Gly	Leu	Gln	Ile	Gly	Glu	Asp	Glu	Asn	Asn	Glu	Asp	Gly	Glu
													245		270
Glu	Glu	Ile	Tyr	Ala	Asp	Lys	Thr	Phe	Gln	Pro	Glu	Pro	Gln	Val	Gly
													250		285
Glu	Glu	Asn	Trp	Gln	Asp	Thr	Asp	Val	Phe	Tyr	Gly	Gly	Arg	Ala	Leu
													255		300
Lys	Lys	Glu	Glu	Lys	Gly	Gly	Gln	Ala	Lys	Phe	Leu	Asn	Gly	Glu	Asn
													260		320
Gly	Gln	Pro	Ser	Lys	Asp	Gln	Asp	Ile	Thr	Leu	Ala	Phe	Phe	Asp	Leu
													265		335
Lys	Gln	Asn	Asp	Thr	Gly	Thr	Thr	Gln	Asn	Gln	Pro	Asp	Val	Val	Met
													270		350
Tyr	Thr	Glu	Asn	Val	Tyr	Leu	Gly	Lys	Glu	Asp	Thr	Ser	Ser	Ala	Ala
													275		365
Asn	Leu	Thr	Asp	Gly	Ser	Gly	Ser	Asn	Thr	Ala	Tyr	Gln	Gly	Val	Lys
													280		380
Tyr	Glu	Asn	Gly	Ala	Gly	Asn	Gly	Ser	Trp	Lys	Val	Asp	Gly	Glu	Val
													285		400
Ala	Ser	Gln	Asn	Gln	Ile	Ala	Lys	Gly	Asn	Leu	Tyr	His	His	His	His
													290		415

His His

<210> SEQ ID NO 46

<211> LENGTH: 418

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 46

Met Ala Asp Glu Ala Pro Thr Asp Lys Glu Arg Gln Asn Gly Gly Gln
 1 5 10 15

Pro Pro Thr Thr Lys Asp Val Thr Lys Thr Phe Gly Val Ala Ala Arg
 20 25 30

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Gly Gly Leu His Ile Thr Asp Lys Gly Leu Gln Ile Gly Glu Asp Glu
 35 40 45
 Asn Asn Glu Asp Gly Glu Glu Glu Ile Tyr Ala Asp Lys Thr Phe Gln
 50 55 60
 Pro Glu Pro Gln Val Gly Glu Glu Asn Trp Gln Asp Thr Asp Val Phe
 65 70 75 80
 Tyr Gly Gly Arg Ala Leu Lys Lys Glu Glu Lys Gly Gly Gln Ala Lys
 85 90 95
 Phe Leu Asn Gly Glu Asn Gly Gln Pro Ser Lys Asp Gln Asp Ile Thr
 100 105 110
 Leu Ala Phe Phe Asp Leu Lys Gln Asn Asp Thr Gly Thr Thr Gln Asn
 115 120 125
 Gln Pro Asp Val Val Met Tyr Thr Glu Asn Val Tyr Leu Gly Lys Glu
 130 135 140
 Asp Thr Ser Ser Ala Ala Asn Leu Thr Asp Gly Ser Gly Ser Asn Thr
 145 150 155 160
 Ala Tyr Gln Gly Val Lys Tyr Glu Asn Gly Ala Gly Asn Gly Ser Trp
 165 170 175
 Lys Val Asp Gly Glu Val Ala Ser Gln Asn Gln Ile Ala Lys Gly Asn
 180 185 190
 Leu Tyr Val Glu Gln Gln Ser Gly Lys Leu Ser Val Asp Thr Lys Ala
 195 200 205
 Pro Leu Gln Val Ala Asn Asp Asn Lys Leu Glu Leu Ser Tyr Asp Asp
 210 215 220
 Pro Phe Lys Val Glu Asn Asn Lys Leu Gly Ile Lys Ala Gly His Gly
 225 230 235 240
 Leu Ala Val Val Thr Lys Glu Asn Thr Ser Leu Pro Ser Leu Val Gly
 245 250 255
 Thr Leu Val Val Gly Ser Ser Ala His Gly Gly Thr Ile Asp Val Arg
 260 265 270
 Leu Gly Glu Gly Gly Gly Leu Ser Phe Asp Glu Lys Gly Thr Val Ser
 275 280 285
 Leu Leu Val Val Thr Gly Lys Tyr Ala Ile Ile Ser Asp Thr Val Asn
 290 295 300
 Pro Lys Gln Phe Ser Ile Lys Leu Leu Phe Asn Asp Lys Gly Val Leu
 305 310 315 320
 Leu Ser Asp Ser Asn Leu Asp Gly Thr Tyr Trp Asn Tyr Arg Ser Asn
 325 330 335
 Asn Asn Asn Ile Gly Thr Pro Tyr Lys Glu Ala Val Gly Phe Met Pro
 340 345 350
 Ser Thr Thr Ala Tyr Pro Lys Pro Thr Asn Asn Thr Ser Thr Asp Pro
 355 360 365
 Asp Lys Lys Val Ser Gln Gly Lys Asn Lys Ile Val Ser Asn Thr Asp
 370 375 380
 Ala Asn Cys Ala Tyr Ser Ile Thr Phe Asp Phe Gly Trp Gly Lys Val
 385 390 395 400
 Tyr Lys Asp Pro Ile Pro Tyr Asp Thr Ser Ser Phe His His His His
 405 410 415
 His His

<210> SEQ ID NO 47

<211> LENGTH: 166

<212> TYPE: PRT

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<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 47

Met Ala Asp Glu Ala Pro Arg Thr Tyr Phe Gly Ile Pro Cys Arg His
1          5          10          15
Gln Ile His Lys Thr Ile Asn Phe Thr Phe Glu Glu Gln Val Asn Phe
          20          25          30
Thr Cys Lys Pro His Lys Lys Tyr Val Thr Trp Phe Tyr Gln Asn Thr
          35          40          45
Thr Thr Val Ala Pro Glu Thr Asn Leu Leu Ser Asp Thr Asn Thr Pro
50          55          60
Lys Thr Gly Gly Glu Leu Trp Val Pro Ser Leu Thr Glu Gly Gly Ser
65          70          75          80
His Ile Glu Ala Ala Pro Lys Pro Glu Val Tyr Thr Gln Val Asn Val
          85          90          95
Thr Arg Gly Gly Asn Ala Thr Leu Asp Gly Pro Phe Asn Asn Asn Thr
          100          105          110
Trp Thr Arg Tyr His Asp Asp Gly Arg Lys Asn Gly Trp Met Phe Asn
          115          120          125
Ile Ser Ser Gly Lys Tyr Lys Val Gln Ser Tyr Thr Asn Ser Tyr Asn
130          135          140
Gly Leu Asp Gly Tyr Glu Lys Leu Glu Val Lys Met Phe Asn Leu Thr
145          150          155          160
His His His His His His
          165

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<210> SEQ ID NO 48
<211> LENGTH: 315
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 48

Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser
1          5          10          15
Ala Ser Ala Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln
          20          25          30
Ile Pro Ala Glu Ala Val Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe
          35          40          45
Asp Val Ala Val Leu Pro Phe Ser Asn Ser Thr Asn Asn Gly Leu Leu
50          55          60
Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys Glu Glu Gly Val
65          70          75          80
Ser Leu Asp Lys Arg Glu Ala Glu Ala Thr Ser Val Glu Gln Gln Ser
          85          90          95
Gly Lys Leu Ser Val Asp Thr Lys Ala Pro Leu Gln Val Ala Asn Asp
100          105          110
Asn Lys Leu Glu Leu Ser Tyr Asp Asp Pro Phe Lys Val Glu Asn Asn
115          120          125
Lys Leu Gly Ile Lys Ala Gly His Gly Leu Ala Val Val Thr Lys Glu
130          135          140
Asn Thr Ser Leu Pro Ser Leu Val Gly Thr Leu Val Val Gly Ser Ser
145          150          155          160

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Ala His Gly Gly Thr Ile Asp Val Arg Leu Gly Glu Gly Gly Gly Leu
165 170 175

Ser Phe Asp Glu Lys Gly Thr Val Ser Leu Leu Val Val Thr Gly Lys
180 185 190

Tyr Ala Ile Ile Ser Asp Thr Val Asn Pro Lys Gln Phe Ser Ile Lys
195 200 205

Leu Leu Phe Asn Asp Lys Gly Val Leu Leu Ser Asp Ser Asn Leu Asp
210 215 220

Gly Thr Tyr Trp Asn Tyr Arg Ser Asn Asn Asn Asn Ile Gly Thr Pro
225 230 235 240

Tyr Lys Glu Ala Val Gly Phe Met Pro Ser Thr Thr Ala Tyr Pro Lys
245 250 255

Pro Thr Asn Asn Thr Ser Thr Asp Pro Asp Lys Lys Val Ser Gln Gly
260 265 270

Lys Asn Lys Ile Val Ser Asn Thr Asp Ala Asn Cys Ala Tyr Ser Ile
275 280 285

Thr Phe Asp Phe Gly Trp Gly Lys Val Tyr Lys Asp Pro Ile Pro Tyr
290 295 300

Asp Thr Ser Ser Phe His His His His His His
305 310 315

<210> SEQ ID NO 49
<211> LENGTH: 218
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 49

Val Glu Gln Gln Ser Gly Lys Leu Ser Val Asp Thr Lys Ala Pro Leu
1 5 10 15

Gln Val Ala Asn Asp Asn Lys Leu Glu Leu Ser Tyr Asp Asp Pro Phe
20 25 30

Lys Val Glu Asn Asn Lys Leu Gly Ile Lys Ala Gly His Gly Leu Ala
35 40 45

Val Val Thr Lys Glu Asn Thr Ser Leu Pro Ser Leu Val Gly Thr Leu
50 55 60

Val Val Gly Ser Ser Ala His Gly Gly Thr Ile Asp Val Arg Leu Gly
65 70 75 80

Glu Gly Gly Gly Leu Ser Phe Asp Glu Lys Gly Thr Val Ser Leu Leu
85 90 95

Val Val Thr Gly Lys Tyr Ala Ile Ile Ser Asp Thr Val Asn Pro Lys
100 105 110

Gln Phe Ser Ile Lys Leu Leu Phe Asn Asp Lys Gly Val Leu Leu Ser
115 120 125

Asp Ser Asn Leu Asp Gly Thr Tyr Trp Asn Tyr Arg Ser Asn Asn Asn
130 135 140

Asn Ile Gly Thr Pro Tyr Lys Glu Ala Val Gly Phe Met Pro Ser Thr
145 150 155 160

Thr Ala Tyr Pro Lys Pro Thr Asn Asn Thr Ser Thr Asp Pro Asp Lys
165 170 175

Lys Val Ser Gln Gly Lys Asn Lys Ile Val Ser Asn Thr Asp Ala Asn
180 185 190

Cys Ala Tyr Ser Ile Thr Phe Asp Phe Gly Trp Gly Lys Val Tyr Lys
195 200 205

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Asp Pro Ile Pro Tyr Asp Thr Ser Ser Phe
210 215

<210> SEQ ID NO 50
 <211> LENGTH: 285
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 50

Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser
1 5 10 15
 Ala Ser Ala Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln
20 25 30
 Ile Pro Ala Glu Ala Val Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe
35 40 45
 Asp Val Ala Val Leu Pro Phe Ser Asn Ser Thr Asn Asn Gly Leu Leu
50 55 60
 Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys Glu Glu Gly Val
65 70 75 80
 Ser Leu Asp Lys Arg Glu Ala Glu Ala Thr Ser Thr Asp Lys Glu Arg
85 90 95
 Gln Asn Gly Gly Gln Pro Pro Thr Thr Lys Asp Val Thr Lys Thr Phe
100 105 110
 Gly Val Ala Ala Arg Gly Gly Leu His Ile Thr Asp Lys Gly Leu Gln
115 120 125
 Ile Gly Glu Asp Glu Asn Asn Glu Asp Gly Glu Glu Glu Ile Tyr Ala
130 135 140
 Asp Lys Thr Phe Gln Pro Glu Pro Gln Val Gly Glu Glu Asn Trp Gln
145 150 155 160
 Asp Thr Asp Val Phe Tyr Gly Gly Arg Ala Leu Lys Lys Glu Glu Lys
165 170 175
 Gly Gly Gln Ala Lys Phe Leu Asn Gly Glu Asn Gly Gln Pro Ser Lys
180 185 190
 Asp Gln Asp Ile Thr Leu Ala Phe Phe Asp Leu Lys Gln Asn Asp Thr
195 200 205
 Gly Thr Thr Gln Asn Gln Pro Asp Val Val Met Tyr Thr Glu Asn Val
210 215 220
 Tyr Leu Gly Lys Glu Asp Thr Ser Ser Ala Ala Asn Leu Thr Asp Gly
225 230 235 240
 Ser Gly Ser Asn Thr Ala Tyr Gln Gly Val Lys Tyr Glu Asn Gly Ala
245 250 255
 Gly Asn Gly Ser Trp Lys Val Asp Gly Glu Val Ala Ser Gln Asn Gln
260 265 270
 Ile Ala Lys Gly Asn Leu Tyr His His His His His His
275 280 285

<210> SEQ ID NO 51
 <211> LENGTH: 188
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 51

Thr Asp Lys Glu Arg Gln Asn Gly Gly Gln Pro Pro Thr Thr Lys Asp
1 5 10 15

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Val Thr Lys Thr Phe Gly Val Ala Ala Arg Gly Gly Leu His Ile Thr
 20 25 30
 Asp Lys Gly Leu Gln Ile Gly Glu Asp Glu Asn Asn Glu Asp Gly Glu
 35 40 45
 Glu Glu Ile Tyr Ala Asp Lys Thr Phe Gln Pro Glu Pro Gln Val Gly
 50 55 60
 Glu Glu Asn Trp Gln Asp Thr Asp Val Phe Tyr Gly Gly Arg Ala Leu
 65 70 75 80
 Lys Lys Glu Glu Lys Gly Gly Gln Ala Lys Phe Leu Asn Gly Glu Asn
 85 90 95
 Gly Gln Pro Ser Lys Asp Gln Asp Ile Thr Leu Ala Phe Phe Asp Leu
 100 105 110
 Lys Gln Asn Asp Thr Gly Thr Thr Gln Asn Gln Pro Asp Val Val Met
 115 120 125
 Tyr Thr Glu Asn Val Tyr Leu Gly Lys Glu Asp Thr Ser Ser Ala Ala
 130 135 140
 Asn Leu Thr Asp Gly Ser Gly Ser Asn Thr Ala Tyr Gln Gly Val Lys
 145 150 155 160
 Tyr Glu Asn Gly Ala Gly Asn Gly Ser Trp Lys Val Asp Gly Glu Val
 165 170 175
 Ala Ser Gln Asn Gln Ile Ala Lys Gly Asn Leu Tyr
 180 185

<210> SEQ ID NO 52
 <211> LENGTH: 1040
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 52

Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser
 1 5 10 15
 Ala Ser Ala Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln
 20 25 30
 Ile Pro Ala Glu Ala Val Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe
 35 40 45
 Asp Val Ala Val Leu Pro Phe Ser Asn Ser Thr Asn Asn Gly Leu Leu
 50 55 60
 Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys Glu Glu Gly Val
 65 70 75 80
 Ser Leu Asp Lys Arg Glu Ala Glu Ala Thr Ser Ala Thr Pro Ser Met
 85 90 95
 Met Pro Gln Trp Ala Tyr Met His Ile Ala Gly Gln Asp Ala Ser Glu
 100 105 110
 Tyr Leu Ser Pro Gly Leu Val Gln Phe Ala Arg Ala Thr Asp Thr Tyr
 115 120 125
 Phe Ser Leu Gly Asn Lys Phe Arg Asn Pro Thr Val Ala Pro Thr His
 130 135 140
 Asp Val Thr Thr Asp Arg Ser Gln Arg Leu Thr Leu Arg Phe Val Pro
 145 150 155 160
 Val Asp Arg Glu Asp Thr Thr Tyr Ser Tyr Lys Ala Arg Phe Thr Leu
 165 170 175
 Ala Val Gly Asp Asn Arg Val Leu Asp Met Ala Ser Thr Tyr Phe Asp
 180 185 190

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Ile	Arg	Gly	Val	Leu	Asp	Arg	Gly	Pro	Ser	Phe	Lys	Pro	Tyr	Ser	Gly
	195						200					205			
Thr	Ala	Tyr	Asn	Ser	Leu	Ala	Pro	Lys	Gly	Ala	Pro	Asn	Ser	Ser	Gln
	210					215					220				
Trp	Thr	Asp	Lys	Glu	Arg	Gln	Asn	Gly	Gly	Gln	Pro	Pro	Thr	Thr	Lys
225					230					235					240
Asp	Val	Thr	Lys	Thr	Phe	Gly	Val	Ala	Ala	Arg	Gly	Gly	Leu	His	Ile
				245						250				255	
Thr	Asp	Lys	Gly	Leu	Gln	Ile	Gly	Glu	Asp	Glu	Asn	Asn	Glu	Asp	Gly
			260					265					270		
Glu	Glu	Glu	Ile	Tyr	Ala	Asp	Lys	Thr	Phe	Gln	Pro	Glu	Pro	Gln	Val
		275					280					285			
Gly	Glu	Glu	Asn	Trp	Gln	Asp	Thr	Asp	Val	Phe	Tyr	Gly	Gly	Arg	Ala
	290					295					300				
Leu	Lys	Lys	Glu	Thr	Lys	Met	Lys	Pro	Cys	Tyr	Gly	Ser	Phe	Ala	Arg
305					310					315					320
Pro	Thr	Asn	Glu	Lys	Gly	Gly	Gln	Ala	Lys	Phe	Leu	Asn	Gly	Glu	Asn
				325					330					335	
Gly	Gln	Pro	Ser	Lys	Asp	Gln	Asp	Ile	Thr	Leu	Ala	Phe	Phe	Asp	Leu
			340					345					350		
Lys	Gln	Asn	Asp	Thr	Gly	Thr	Thr	Gln	Asn	Gln	Pro	Asp	Val	Val	Met
		355					360					365			
Tyr	Thr	Glu	Asn	Val	Tyr	Leu	Glu	Thr	Pro	Asp	Thr	His	Val	Val	Tyr
	370					375				380					
Lys	Pro	Gly	Lys	Glu	Asp	Thr	Ser	Ser	Ala	Ala	Asn	Leu	Thr	Gln	Gln
385					390					395					400
Ser	Met	Pro	Asn	Arg	Pro	Asn	Tyr	Ile	Gly	Phe	Arg	Asp	Asn	Phe	Val
				405					410					415	
Gly	Leu	Met	Tyr	Tyr	Asn	Ser	Thr	Gly	Asn	Met	Gly	Val	Leu	Ala	Gly
			420					425					430		
Gln	Ala	Ser	Gln	Leu	Asn	Ala	Val	Val	Asp	Leu	Gln	Asp	Arg	Asn	Thr
		435				440						445			
Glu	Leu	Ser	Tyr	Gln	Leu	Leu	Leu	Asp	Ser	Leu	Gly	Asp	Arg	Thr	Arg
	450					455					460				
Tyr	Phe	Ser	Met	Trp	Asn	Ser	Ala	Val	Asp	Ser	Tyr	Asp	Pro	Asp	Val
465					470					475					480
Arg	Ile	Ile	Glu	Asn	His	Gly	Val	Glu	Asp	Glu	Leu	Pro	Asn	Tyr	Cys
				485					490					495	
Phe	Pro	Leu	Asp	Gly	Ser	Gly	Ser	Asn	Thr	Ala	Tyr	Gln	Gly	Val	Lys
		500						505					510		
Tyr	Glu	Asn	Gly	Ala	Gly	Asn	Gly	Ser	Trp	Lys	Val	Asp	Gly	Glu	Val
		515					520					525			
Ala	Ser	Gln	Asn	Gln	Ile	Ala	Lys	Gly	Asn	Leu	Tyr	Ala	Met	Glu	Ile
	530					535					540				
Asn	Leu	Gln	Ala	Asn	Leu	Trp	Lys	Ser	Phe	Leu	Tyr	Ser	Asn	Val	Ala
545					550					555					560
Leu	Tyr	Leu	Pro	Asp	Ser	Tyr	Lys	Tyr	Thr	Pro	Ala	Asn	Ile	Thr	Leu
				565					570					575	
Pro	Thr	Asn	Thr	Asn	Thr	Tyr	Glu	Tyr	Met	Asn	Gly	Arg	Val	Val	Ala
			580					585					590		
Pro	Ser	Leu	Val	Asp	Ala	Tyr	Val	Asn	Ile	Gly	Ala	Arg	Trp	Ser	Leu
	595						600					605			

Asp	Pro	Met	Asp	Asn	Val	Asn	Pro	Phe	Asn	His	His	Arg	Asn	Ala	Gly
610						615				620					
Leu	Arg	Tyr	Arg	Ser	Met	Leu	Leu	Gly	Asn	Gly	Arg	Tyr	Val	Pro	Phe
625					630					635					640
His	Ile	Gln	Val	Pro	Gln	Lys	Phe	Phe	Ala	Ile	Lys	Asn	Leu	Leu	Leu
				645					650					655	
Leu	Pro	Gly	Ser	Tyr	Thr	Tyr	Glu	Trp	Asn	Phe	Arg	Lys	Asp	Val	Asn
			660					665					670		
Met	Ile	Leu	Gln	Ser	Ser	Leu	Gly	Asn	Asp	Leu	Arg	Val	Asp	Gly	Ala
675							680					685			
Ser	Val	Arg	Phe	Asp	Ser	Val	Asn	Leu	Tyr	Ala	Thr	Phe	Phe	Pro	Met
690						695					700				
Ala	His	Asn	Thr	Ala	Ser	Thr	Leu	Glu	Ala	Met	Leu	Arg	Asn	Asp	Thr
705					710					715					720
Asn	Asp	Gln	Ser	Phe	Asn	Asp	Tyr	Leu	Ser	Ala	Ala	Asn	Met	Leu	Tyr
				725					730					735	
Pro	Ile	Pro	Ala	Lys	Ala	Thr	Asn	Val	Pro	Ile	Ser	Ile	Pro	Ser	Arg
			740					745					750		
Asn	Trp	Ala	Ala	Phe	Arg	Gly	Trp	Ser	Phe	Thr	Arg	Leu	Lys	Thr	Lys
755							760					765			
Glu	Thr	Pro	Ser	Leu	Gly	Ser	Gly	Phe	Asp	Pro	Tyr	Phe	Val	Tyr	Ser
770						775					780				
Gly	Ser	Ile	Pro	Tyr	Leu	Asp	Gly	Thr	Phe	Tyr	Leu	Asn	His	Thr	Phe
785					790					795					800
Lys	Lys	Val	Ser	Ile	Met	Phe	Asp	Ser	Ser	Val	Ser	Trp	Pro	Gly	Asn
				805					810					815	
Asp	Arg	Leu	Leu	Thr	Pro	Asn	Glu	Phe	Glu	Ile	Lys	Arg	Ser	Val	Asp
			820					825					830		
Gly	Glu	Gly	Tyr	Asn	Val	Ala	Gln	Cys	Asn	Met	Thr	Lys	Asp	Trp	Phe
835							840					845			
Leu	Val	Gln	Met	Leu	Ser	His	Tyr	Asn	Ile	Gly	Tyr	Gln	Gly	Phe	Tyr
850						855					860				
Val	Pro	Glu	Gly	Tyr	Lys	Asp	Arg	Met	Tyr	Ser	Phe	Phe	Arg	Asn	Phe
865					870					875					880
Gln	Pro	Met	Ser	Arg	Gln	Val	Val	Asp	Glu	Ile	Asn	Tyr	Lys	Asp	Tyr
				885					890					895	
Lys	Ala	Val	Thr	Leu	Pro	Phe	Gln	His	Asn	Asn	Ser	Gly	Phe	Thr	Gly
			900					905					910		
Tyr	Leu	Ala	Pro	Thr	Met	Arg	Gln	Gly	Gln	Pro	Tyr	Pro	Ala	Asn	Phe
915							920					925			
Pro	Tyr	Pro	Leu	Ile	Gly	Gln	Thr	Ala	Val	Pro	Ser	Val	Thr	Gln	Lys
930						935					940				
Lys	Phe	Leu	Cys	Asp	Arg	Val	Met	Trp	Arg	Ile	Pro	Phe	Ser	Ser	Asn
945					950					955					960
Phe	Met	Ser	Met	Gly	Ala	Leu	Thr	Asp	Leu						

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1025	1030	1035
His His		
1040		
<210> SEQ ID NO 53		
<211> LENGTH: 943		
<212> TYPE: PRT		
<213> ORGANISM: Artificial		
<220> FEATURE:		
<223> OTHER INFORMATION: Synthetic Polypeptide		
<400> SEQUENCE: 53		
Ala Thr Pro Ser Met Met Pro Gln Trp Ala Tyr Met His Ile Ala Gly		
1 5 10 15		
Gln Asp Ala Ser Glu Tyr Leu Ser Pro Gly Leu Val Gln Phe Ala Arg		
20 25 30		
Ala Thr Asp Thr Tyr Phe Ser Leu Gly Asn Lys Phe Arg Asn Pro Thr		
35 40 45		
Val Ala Pro Thr His Asp Val Thr Thr Asp Arg Ser Gln Arg Leu Thr		
50 55 60		
Leu Arg Phe Val Pro Val Asp Arg Glu Asp Thr Thr Tyr Ser Tyr Lys		
65 70 75 80		
Ala Arg Phe Thr Leu Ala Val Gly Asp Asn Arg Val Leu Asp Met Ala		
85 90 95		
Ser Thr Tyr Phe Asp Ile Arg Gly Val Leu Asp Arg Gly Pro Ser Phe		
100 105 110		
Lys Pro Tyr Ser Gly Thr Ala Tyr Asn Ser Leu Ala Pro Lys Gly Ala		
115 120 125		
Pro Asn Ser Ser Gln Trp Thr Asp Lys Glu Arg Gln Asn Gly Gly Gln		
130 135 140		
Pro Pro Thr Thr Lys Asp Val Thr Lys Thr Phe Gly Val Ala Ala Arg		
145 150 155 160		
Gly Gly Leu His Ile Thr Asp Lys Gly Leu Gln Ile Gly Glu Asp Glu		
165 170 175		
Asn Asn Glu Asp Gly Glu Glu Glu Ile Tyr Ala Asp Lys Thr Phe Gln		
180 185 190		
Pro Glu Pro Gln Val Gly Glu Glu Asn Trp Gln Asp Thr Asp Val Phe		
195 200 205		
Tyr Gly Gly Arg Ala Leu Lys Lys Glu Thr Lys Met Lys Pro Cys Tyr		
210 215 220		
Gly Ser Phe Ala Arg Pro Thr Asn Glu Lys Gly Gly Gln Ala Lys Phe		
225 230 235 240		
Leu Asn Gly Glu Asn Gly Gln Pro Ser Lys Asp Gln Asp Ile Thr Leu		
245 250 255		
Ala Phe Phe Asp Leu Lys Gln Asn Asp Thr Gly Thr Thr Gln Asn Gln		
260 265 270		
Pro Asp Val Val Met Tyr Thr Glu Asn Val Tyr Leu Glu Thr Pro Asp		
275 280 285		
Thr His Val Val Tyr Lys Pro Gly Lys Glu Asp Thr Ser Ser Ala Ala		
290 295 300		
Asn Leu Thr Gln Gln Ser Met Pro Asn Arg Pro Asn Tyr Ile Gly Phe		
305 310 315 320		
Arg Asp Asn Phe Val Gly Leu Met Tyr Tyr Asn Ser Thr Gly Asn Met		
325 330 335		
Gly Val Leu Ala Gly Gln Ala Ser Gln Leu Asn Ala Val Val Asp Leu		

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340					345					350					
Gln	Asp	Arg	Asn	Thr	Glu	Leu	Ser	Tyr	Gln	Leu	Leu	Leu	Asp	Ser	Leu
		355					360					365			
Gly	Asp	Arg	Thr	Arg	Tyr	Phe	Ser	Met	Trp	Asn	Ser	Ala	Val	Asp	Ser
	370					375					380				
Tyr	Asp	Pro	Asp	Val	Arg	Ile	Ile	Glu	Asn	His	Gly	Val	Glu	Asp	Glu
	385				390					395					400
Leu	Pro	Asn	Tyr	Cys	Phe	Pro	Leu	Asp	Gly	Ser	Gly	Ser	Asn	Thr	Ala
				405					410					415	
Tyr	Gln	Gly	Val	Lys	Tyr	Glu	Asn	Gly	Ala	Gly	Asn	Gly	Ser	Trp	Lys
			420					425					430		
Val	Asp	Gly	Glu	Val	Ala	Ser	Gln	Asn	Gln	Ile	Ala	Lys	Gly	Asn	Leu
		435					440					445			
Tyr	Ala	Met	Glu	Ile	Asn	Leu	Gln	Ala	Asn	Leu	Trp	Lys	Ser	Phe	Leu
	450					455					460				
Tyr	Ser	Asn	Val	Ala	Leu	Tyr	Leu	Pro	Asp	Ser	Tyr	Lys	Tyr	Thr	Pro
	465				470					475					480
Ala	Asn	Ile	Thr	Leu	Pro	Thr	Asn	Thr	Asn	Thr	Tyr	Glu	Tyr	Met	Asn
				485					490					495	
Gly	Arg	Val	Val	Ala	Pro	Ser	Leu	Val	Asp	Ala	Tyr	Val	Asn	Ile	Gly
			500						505					510	
Ala	Arg	Trp	Ser	Leu	Asp	Pro	Met	Asp	Asn	Val	Asn	Pro	Phe	Asn	His
		515					520					525			
His	Arg	Asn	Ala	Gly	Leu	Arg	Tyr	Arg	Ser	Met	Leu	Leu	Gly	Asn	Gly
	530					535					540				
Arg	Tyr	Val	Pro	Phe	His	Ile	Gln	Val	Pro	Gln	Lys	Phe	Phe	Ala	Ile
	545				550					555					560
Lys	Asn	Leu	Leu	Leu	Leu	Pro	Gly	Ser	Tyr	Thr	Tyr	Glu	Trp	Asn	Phe
				565					570					575	
Arg	Lys	Asp	Val	Asn	Met	Ile	Leu	Gln	Ser	Ser	Leu	Gly	Asn	Asp	Leu
			580					585						590	
Arg	Val	Asp	Gly	Ala	Ser	Val	Arg	Phe	Asp	Ser	Val	Asn	Leu	Tyr	Ala
		595					600					605			
Thr	Phe	Phe	Pro	Met	Ala	His	Asn	Thr	Ala	Ser	Thr	Leu	Glu	Ala	Met
	610					615					620				
Leu	Arg	Asn	Asp	Thr	Asn	Asp	Gln	Ser	Phe	Asn	Asp	Tyr	Leu	Ser	Ala
	625				630					635					640
Ala	Asn	Met	Leu	Tyr	Pro	Ile	Pro	Ala	Lys	Ala	Thr	Asn	Val	Pro	Ile
				645					650					655	
Ser	Ile	Pro	Ser	Arg	Asn	Trp	Ala	Ala	Phe	Arg	Gly	Trp	Ser	Phe	Thr
		660					665						670		
Arg	Leu	Lys	Thr	Lys	Glu	Thr	Pro	Ser	Leu	Gly	Ser	Gly	Phe	Asp	Pro
		675					680					685			
Tyr	Phe	Val	Tyr	Ser	Gly	Ser	Ile	Pro	Tyr	Leu	Asp	Gly	Thr	Phe	Tyr
	690					695					700				
Leu	Asn	His	Thr	Phe	Lys	Lys	Val	Ser	Ile	Met	Phe	Asp	Ser	Ser	Val
	705				710					715					720
Ser	Trp	Pro	Gly	Asn	Asp	Arg	Leu	Leu	Thr	Pro	Asn	Glu	Phe	Glu	Ile
				725					730					735	
Lys	Arg	Ser	Val	Asp	Gly	Glu	Gly	Tyr	Asn	Val	Ala	Gln	Cys	Asn	Met
			740					745					750		
Thr	Lys	Asp	Trp	Phe	Leu	Val	Gln	Met	Leu	Ser	His	Tyr	Asn	Ile	Gly
		755					760					765			

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Tyr Gln Gly Phe Tyr Val Pro Glu Gly Tyr Lys Asp Arg Met Tyr Ser
 770 775 780
 Phe Phe Arg Asn Phe Gln Pro Met Ser Arg Gln Val Val Asp Glu Ile
 785 790 795 800
 Asn Tyr Lys Asp Tyr Lys Ala Val Thr Leu Pro Phe Gln His Asn Asn
 805 810 815
 Ser Gly Phe Thr Gly Tyr Leu Ala Pro Thr Met Arg Gln Gly Gln Pro
 820 825 830
 Tyr Pro Ala Asn Phe Pro Tyr Pro Leu Ile Gly Gln Thr Ala Val Pro
 835 840 845
 Ser Val Thr Gln Lys Lys Phe Leu Cys Asp Arg Val Met Trp Arg Ile
 850 855 860
 Pro Phe Ser Ser Asn Phe Met Ser Met Gly Ala Leu Thr Asp Leu Gly
 865 870 875 880
 Gln Asn Met Leu Tyr Ala Asn Ser Ala His Ala Leu Asp Met Thr Phe
 885 890 895
 Glu Val Asp Pro Met Asp Glu Pro Thr Leu Leu Tyr Leu Leu Phe Glu
 900 905 910
 Val Phe Asp Val Val Arg Val His Gln Pro His Arg Gly Val Ile Glu
 915 920 925
 Ala Val Tyr Leu Arg Thr Pro Phe Ser Ala Gly Asn Ala Thr Thr
 930 935 940

<210> SEQ ID NO 54
 <211> LENGTH: 251
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 54

Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser
 1 5 10 15
 Ala Ser Ala Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln
 20 25 30
 Ile Pro Ala Glu Ala Val Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe
 35 40 45
 Asp Val Ala Val Leu Pro Phe Ser Asn Ser Thr Asn Asn Gly Leu Leu
 50 55 60
 Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys Glu Glu Gly Val
 65 70 75 80
 Ser Leu Asp Lys Arg Glu Ala Glu Ala Thr Ser Arg Thr Tyr Phe Gly
 85 90 95
 Ile Pro Cys Arg His Gln Ile His Lys Thr Ile Asn Phe Thr Phe Glu
 100 105 110
 Glu Gln Val Asn Phe Thr Cys Lys Pro His Lys Lys Tyr Val Thr Trp
 115 120 125
 Phe Tyr Gln Asn Thr Thr Thr Val Ala Pro Glu Thr Asn Leu Leu Ser
 130 135 140
 Asp Thr Asn Thr Pro Lys Thr Gly Gly Glu Leu Trp Val Pro Ser Leu
 145 150 155 160
 Thr Glu Gly Gly Ser His Ile Glu Ala Ala Pro Lys Pro Glu Val Tyr
 165 170 175
 Thr Gln Val Asn Val Thr Arg Gly Gly Asn Ala Thr Leu Asp Gly Pro
 180 185 190

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Phe Asn Asn Asn Thr Trp Thr Arg Tyr His Asp Asp Gly Arg Lys Asn
 195 200 205

Gly Trp Met Phe Asn Ile Ser Ser Gly Lys Tyr Lys Val Gln Ser Tyr
 210 215 220

Thr Asn Ser Tyr Asn Gly Leu Asp Gly Tyr Glu Lys Leu Glu Val Lys
 225 230 235 240

Met Phe Asn Leu Thr His His His His His His
 245 250

<210> SEQ ID NO 55
 <211> LENGTH: 154
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 55

Arg Thr Tyr Phe Gly Ile Pro Cys Arg His Gln Ile His Lys Thr Ile
 1 5 10 15

Asn Phe Thr Phe Glu Glu Gln Val Asn Phe Thr Cys Lys Pro His Lys
 20 25 30

Lys Tyr Val Thr Trp Phe Tyr Gln Asn Thr Thr Thr Val Ala Pro Glu
 35 40 45

Thr Asn Leu Leu Ser Asp Thr Asn Thr Pro Lys Thr Gly Gly Glu Leu
 50 55 60

Trp Val Pro Ser Leu Thr Glu Gly Gly Ser His Ile Glu Ala Ala Pro
 65 70 75 80

Lys Pro Glu Val Tyr Thr Gln Val Asn Val Thr Arg Gly Gly Asn Ala
 85 90 95

Thr Leu Asp Gly Pro Phe Asn Asn Asn Thr Trp Thr Arg Tyr His Asp
 100 105 110

Asp Gly Arg Lys Asn Gly Trp Met Phe Asn Ile Ser Ser Gly Lys Tyr
 115 120 125

Lys Val Gln Ser Tyr Thr Asn Ser Tyr Asn Gly Leu Asp Gly Tyr Glu
 130 135 140

Lys Leu Glu Val Lys Met Phe Asn Leu Thr
 145 150

<210> SEQ ID NO 56
 <211> LENGTH: 89
 <212> TYPE: PRT
 <213> ORGANISM: *Saccharomyces cerevisiae*

<400> SEQUENCE: 56

Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser
 1 5 10 15

Ala Ser Ala Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln
 20 25 30

Ile Pro Ala Glu Ala Val Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe
 35 40 45

Asp Val Ala Val Leu Pro Phe Ser Asn Ser Thr Asn Asn Gly Leu Leu
 50 55 60

Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys Glu Glu Gly Val
 65 70 75 80

Ser Leu Asp Lys Arg Glu Ala Glu Ala
 85

-continued

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<210> SEQ ID NO 57
<211> LENGTH: 89
<212> TYPE: PRT
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 57

Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser
1           5           10           15

Ala Leu Ala Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln
20           25           30

Ile Pro Ala Glu Ala Val Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe
35           40           45

Asp Val Ala Val Leu Pro Phe Ser Asn Ser Thr Asn Asn Gly Leu Leu
50           55           60

Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys Glu Glu Gly Val
65           70           75           80

Ser Leu Asp Lys Arg Glu Ala Glu Ala
85

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<210> SEQ ID NO 58
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Peptide

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<400> SEQUENCE: 58

Met Ala Asp Glu Ala Pro
1           5

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What is claimed is:

1. An immunotherapeutic composition comprising: a) a yeast vehicle; and b) a fusion protein comprising an adenovirus-36 (Ad-36) antigen, wherein the Ad-36 antigen comprises the amino acid sequence SEQ ID NO:55.

2. The immunotherapeutic composition of claim 1, wherein the yeast vehicle is a whole yeast.

3. The immunotherapeutic composition of claim 1, wherein the yeast vehicle is from *Saccharomyces cerevisiae*.

4. A fusion protein, wherein the fusion protein comprises an amino acid sequence that is at least 95% identical to SEQ ID NO:47, SEQ ID NO:54, or SEQ ID NO:55.

5. An immunotherapeutic composition comprising:

a) a yeast vehicle; and

b) a fusion protein comprising an adenovirus-36 (Ad-36) antigen, wherein the fusion protein comprises an amino acid sequence that is at least 95% identical to SEQ ID NO:54 or SEQ ID NO:47.

6. An immunotherapeutic composition comprising:

a) a yeast vehicle; and

b) a fusion protein comprising an adenovirus-36 (Ad-36) antigen, wherein the Ad-36 antigen comprises an amino acid sequence that is at least 95% identical to SEQ ID NO:55.

7. The immunotherapeutic composition of claim 6, wherein the Ad-36 antigen comprises the amino acid sequence SEQ ID NO:55.

8. The immunotherapeutic composition of claim 2, wherein the Ad-36 antigen is expressed by the whole yeast.

9. The immunotherapeutic composition of claim 2, wherein the whole yeast is heat-inactivated.

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10. The immunotherapeutic composition of claim 1, wherein the composition is formulated in a pharmaceutically acceptable excipient suitable for administration to an individual.

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11. The immunotherapeutic composition of claim 1, further comprising at least one biological response modifier.

12. The immunotherapeutic composition of claim 6, wherein the Ad-36 antigen comprises an amino acid sequence that is at least 97% identical to SEQ ID NO:55.

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13. The immunotherapeutic composition of claim 6, wherein the Ad-36 antigen comprises an amino acid sequence that is at least 99% identical to SEQ ID NO:55.

14. The immunotherapeutic composition of claim 5, wherein the fusion protein comprises the amino acid sequence SEQ ID NO:47 or SEQ ID NO:54.

15. The fusion protein of claim 4, wherein the fusion protein comprises an amino acid sequence that is 95% identical to SEQ ID NO:55.

55

16. The fusion protein of claim 4, wherein the fusion protein comprises an amino acid sequence that is 99% identical to SEQ ID NO:55.

17. The fusion protein of claim 4, wherein the fusion protein comprises the amino acid sequence SEQ ID NO:55.

18. The fusion protein of claim 4, wherein the fusion protein comprises the amino acid sequence SEQ ID NO:47 or SEQ ID NO:54.

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19. The immunotherapeutic composition of claim 6, wherein the yeast vehicle is a whole yeast.

20. The immunotherapeutic composition of claim 6, wherein the yeast vehicle is from *Saccharomyces cerevisiae*.

* * * * *